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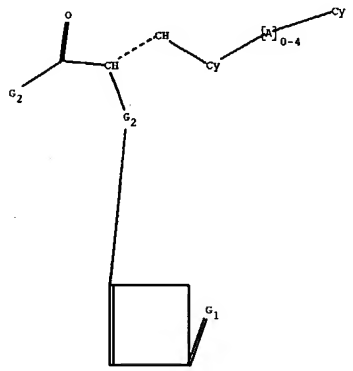
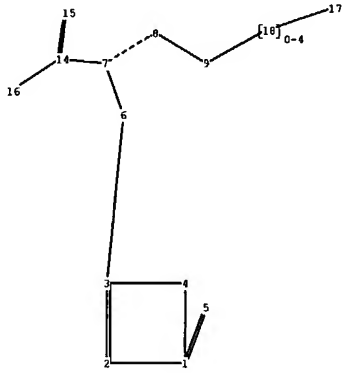




chain nodes :
5 6 7 8 9 14 15 16 17 18
ring nodes :
1 2 3 4
chain bonds :
1-5 3-6 6-7 7-8 7-14 8-9 9-18 14-15 14-16 17-18
ring bonds :
1-2 1-4 2-3 3-4
exact/norm bonds :
1-5 3-6 6-7 7-8 8-9 9-18 14-15 14-16 17-18
exact bonds :
1-2 1-4 2-3 3-4 7-14
isolated ring systems :
containing 1 :

G1:O,S

G2:O,S,N

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:CLASS 6:CLASS 7:CLASS 8:CLASS
9:Atom 14:CLASS 15:CLASS 16:CLASS 17:Atom 18:CLASS

\

10/081,072

STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.

=> s l10 sss full
FULL SEARCH INITIATED 12:03:33 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 73051 TO ITERATE

100.0% PROCESSED 73051 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.02

L11 0 SEA SSS FUL L10

Spiro

=>
Uploading C:\Program Files\Stnexp\Queries\081072.str

L12 STRUCTURE UPLOADED

=> d l12
L12 HAS NO ANSWERS
L12 STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.

=> s l12 sss full
FULL SEARCH INITIATED 12:06:03 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 1009 TO ITERATE

100.0% PROCESSED 1009 ITERATIONS 756 ANSWERS
SEARCH TIME: 00.00.01

L13 756 SEA SSS FUL L12

=> file caplus
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	625.04	965.51

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-4.16

FILE 'CAPLUS' ENTERED AT 12:06:09 ON 25 JUN 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 25 Jun 2004 VOL 141 ISS 1
FILE LAST UPDATED: 24 Jun 2004 (20040624/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l13
L14 14 L13

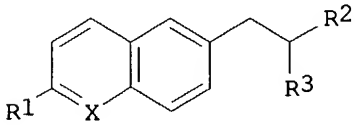
=> d l14 1-14 ibib abs hitstr

L14 ANSWER 1 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:892751 CAPLUS
DOCUMENT NUMBER: 139:381384
TITLE: Preparation of 2,6-quinolinyl and 2,6-naphthyl(acylamino)propionic acids as VLA-4 inhibitors
INVENTOR(S): Lassoie, Marie-Agnes; Knerr, Laurent; Demaude, Thierry; De Laveleye, Francoise; Kogej, Thierry; Routier, Sylvain; Guillaumet, Gerald
PATENT ASSIGNEE(S): UCB, S.A., Belg.
SOURCE: PCT Int. Appl., 122 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003093237	A1	20031113	WO 2003-EP3909	20030415

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: EP 2002-9746 A 20020430
OTHER SOURCE(S): MARPAT 139:381384
GI



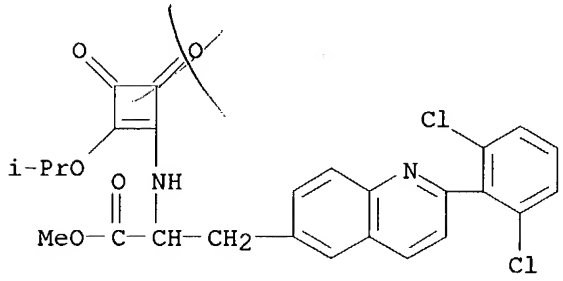
I

AB Title compds. I [X = N, CH; R1 = R1 = cycloalkyl, aryl, hewterocyclic,

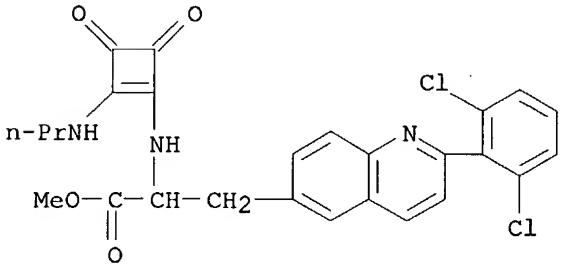
heterocyclylalkyl, substituted OH, norbornen-5-yl; R2 = (un)substituted NH2, OH, CONH2; R3 = tetrazolyl, CN, CH2OH, (un)substituted CO2H] were prepared for use in treating VLA-4 dependent inflammatory diseases such as asthma, allergic rhinitis, sinusitis, conjunctivitis, food allergy, psoriasis, urticaria, pruritus, eczema, rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis and atherosclerosis (no data). Thus, 4-nitrophenylalanine was esterified, N-protected , reduced to the amine, cyclized with 2,6-Cl2C6H3CHO and CH2:CHSPh, followed by elimination of PhSH to give I [X = N, R1 = 2,6-Cl2C6H3, R2 = NHBoc, R3 = CO2Me]. This compound was deprotected and acylated with 2,6-Cl2C6H3COCl, followed by ester hydrolysis to give I [X = N, R1 = 2,6=Cl2C6H3, R2 = 2,6-Cl2C6H3CONH, R3 = CO2H].

IT **623145-12-0P 623145-19-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of 2,6-quinolinyl and 2,6-naphthyl(acylamino)propionic acids as VLA-4 inhibitors)

RN 623145-12-0 CAPLUS
CN 6-Quinolinepropanoic acid, 2-(2,6-dichlorophenyl)-α-[[2-(1-methylethoxy)-3,4-dioxo-1-cyclobuten-1-yl]amino]-, methyl ester (9CI) (CA INDEX NAME)



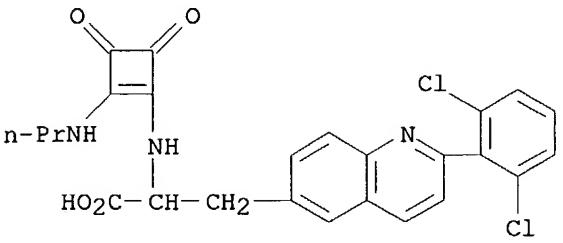
RN 623145-19-7 CAPLUS
CN 6-Quinolinepropanoic acid, 2-(2,6-dichlorophenyl)-α-[[3,4-dioxo-2-(propylamino)-1-cyclobuten-1-yl]amino]-, methyl ester (9CI) (CA INDEX NAME)



IT **623146-06-5P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 2,6-quinolinyl and 2,6-naphthyl(acylamino)propionic acids as VLA-4 inhibitors)

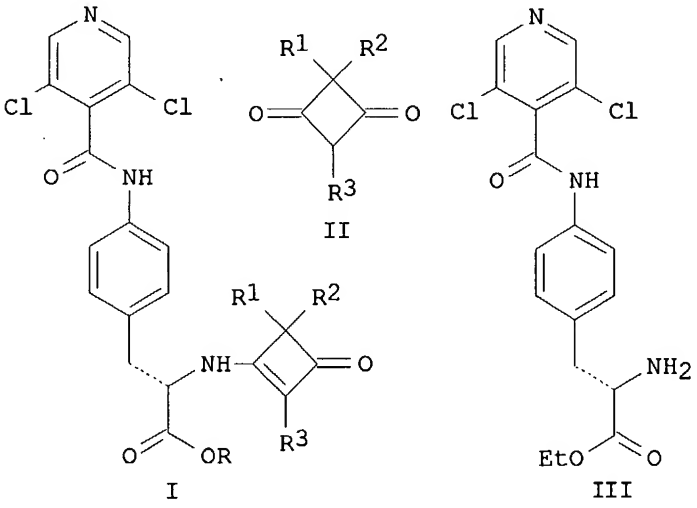
RN 623146-06-5 CAPLUS
CN 6-Quinolinepropanoic acid, 2-(2,6-dichlorophenyl)-α-[[3,4-dioxo-2-

(propylamino)-1-cyclobuten-1-yl]amino]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 2 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:435940 CAPLUS
DOCUMENT NUMBER: 139:149503
TITLE: Efficient Synthesis of 3-Aminocyclobut-2-en-1-ones: Squaramide Surrogates as Potent VLA-4 Antagonists
AUTHOR(S): Brand, Stephen; De Candole, Benjamin C.; Brown, Julien A.
CORPORATE SOURCE: Medicinal Chemistry, Celltech Group plc, Slough, SL1 4EN, UK
SOURCE: Organic Letters (2003), 5(13), 2343-2346
CODEN: ORLEF7; ISSN: 1523-7060
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 139:149503
GI



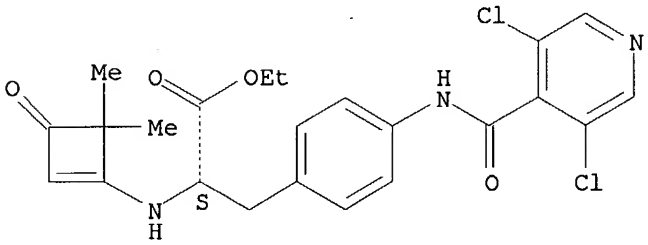
AB A novel series of uniquely functionalized 3-aminocyclobut-2-en-1-ones I [R = Et, R1 = Me, R2 = Me, Ph, CH2Ph, R3 = H; R = Et, R1R2 = (CH2)n, n = 4-6, R3 = H; R = Et, R1R2 = (CH2)2O(CH2)2, R3 = H; R = Et, R1 = R2 = Me, R3 = CH2Ph, Me, n-Pr, etc.; etc.] has been prepared by facile condensation of a

variety of cyclobuta-1,3-diones II with a phenylalanine-derived primary amine III. These systems subsequently lend themselves to substitution at C-2 by reaction with a variety of electrophilic reagents including N-halosuccinimides, sulfenyl chlorides, and Eschenmoser's salt, to get new analogs I [R = Et, R1R2 = (CH2)5, R3 = Br, SPh, SePh, etc.]. Compds. I (R = H) from this novel series are potent antagonists of VLA-4.

IT **455262-11-0P 455262-24-5P 455262-34-7P**
455263-48-6P 455263-52-2P 455263-71-5P
455263-73-7P 455263-75-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of phenylalanine-derived 3-aminocyclobut-2-en-1-ones as VLA-4 antagonists)

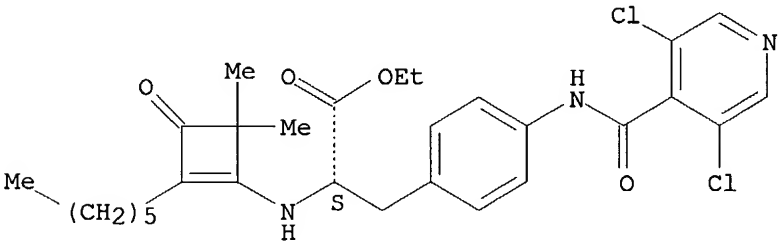
RN 455262-11-0 CAPLUS
CN L-Phenylalanine, 4-[[(3,5-dichloro-4-pyridinyl)carbonyl]amino]-N-(4,4-dimethyl-3-oxo-1-cyclobuten-1-yl)-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



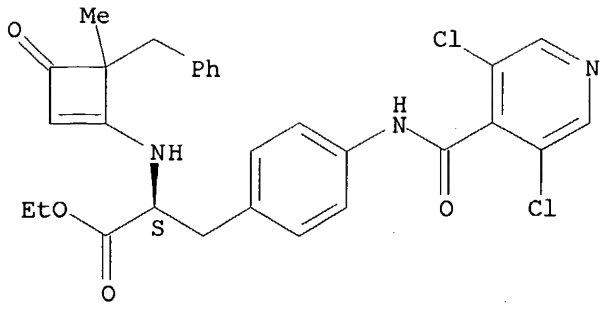
RN 455262-24-5 CAPLUS
CN L-Phenylalanine, 4-[[(3,5-dichloro-4-pyridinyl)carbonyl]amino]-N-(2-hexyl-4,4-dimethyl-3-oxo-1-cyclobuten-1-yl)-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



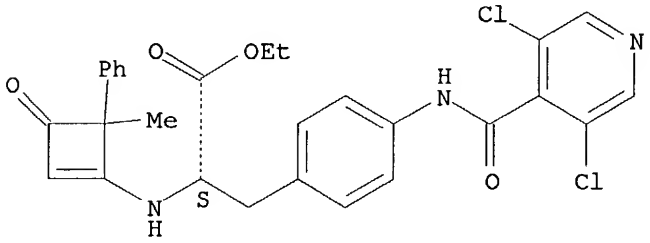
RN 455262-34-7 CAPLUS
CN L-Phenylalanine, 4-[[(3,5-dichloro-4-pyridinyl)carbonyl]amino]-N-[4-methyl-3-oxo-4-(phenylmethyl)-1-cyclobuten-1-yl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



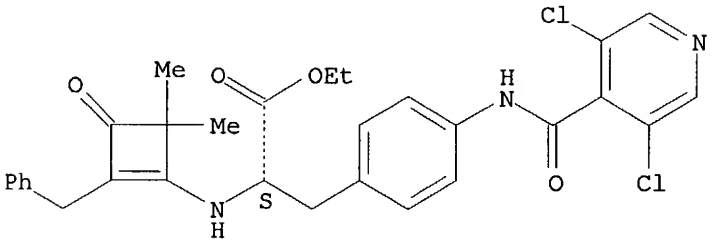
RN 455263-48-6 CAPLUS
CN L-Phenylalanine, 4-[[(3,5-dichloro-4-pyridinyl)carbonyl]amino]-N-(4-methyl-3-oxo-4-phenyl-1-cyclobuten-1-yl)-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



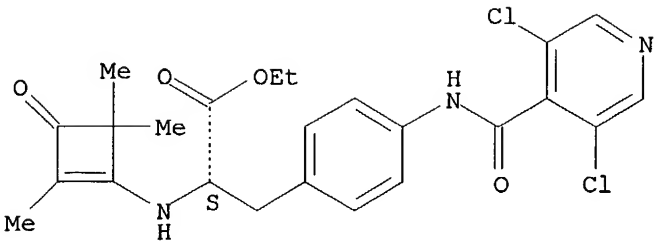
RN 455263-52-2 CAPLUS
CN L-Phenylalanine, 4-[[(3,5-dichloro-4-pyridinyl)carbonyl]amino]-N-[4,4-dimethyl-3-oxo-2-(phenylmethyl)-1-cyclobuten-1-yl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



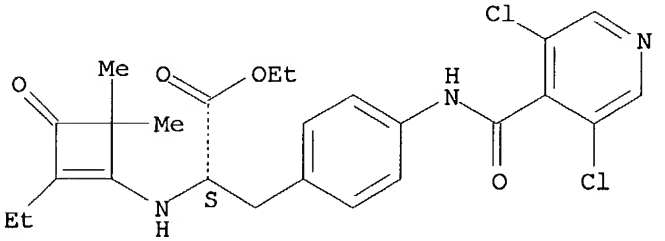
RN 455263-71-5 CAPLUS
CN L-Phenylalanine, 4-[[(3,5-dichloro-4-pyridinyl)carbonyl]amino]-N-(2,4,4-trimethyl-3-oxo-1-cyclobuten-1-yl)-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



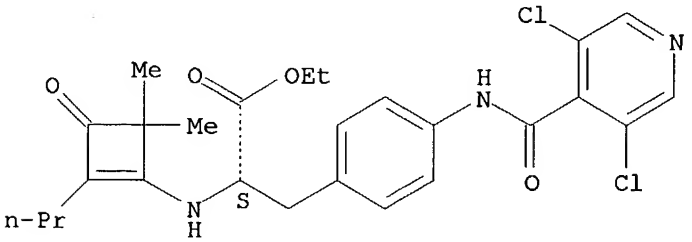
RN 455263-73-7 CAPLUS
CN L-Phenylalanine, 4-[[(3,5-dichloro-4-pyridinyl)carbonyl]amino]-N-(2-ethyl-4,4-dimethyl-3-oxo-1-cyclobuten-1-yl)-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 455263-75-9 CAPLUS
CN L-Phenylalanine, 4-[[(3,5-dichloro-4-pyridinyl)carbonyl]amino]-N-(4,4-dimethyl-3-oxo-2-propyl-1-cyclobuten-1-yl)-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 3 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:117787 CAPLUS
DOCUMENT NUMBER: 138:137592
TITLE: Preparation of bicyclic heteroaromatic alanines as α4-integrin inhibitors
INVENTOR(S): Aujla, Pavandeep; Norman, Timothy John; Porter, John Robert; Bailey, Stuart; Brand, Stephen
PATENT ASSIGNEE(S): Celltech R & D Limited, UK
SOURCE: PCT Int. Appl., 97 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

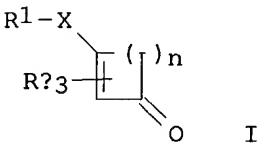
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003011815	A1	20030213	WO 2002-GB3400	20020725

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2001-18241 A 20010726
GB 2001-26653 A 20011106

OTHER SOURCE(S): MARPAT 138:137592
GI



I

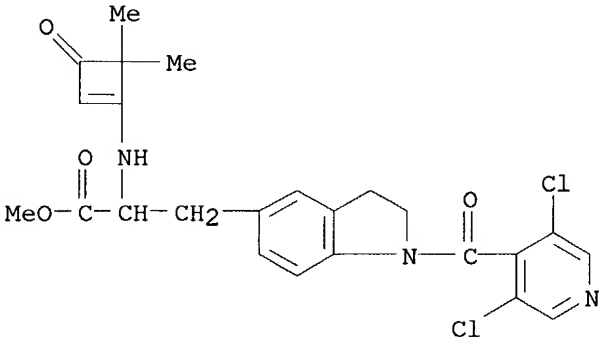
AB Compds. I [n = 1-4; X is O, S, NH, or alkylimino; R1 is a group Ar1-L2-Ar2-Alk-, in which Ar1 is an optionally-substituted (hetero)aromatic group, L2 is a covalent bond or a linker atom or group, Ar2 is an optionally substituted bicyclic heteroarylene group, and Alk is a chain CH2CHR, CH=CR, or CH(CH2R) (R is CO2H or a derivative or biostere); Rx are independently groups L1-Alk10-1-R31-3, in which L1 is a covalent bond or a linker atom or group, Alk1 is an optionally substituted (hetero)aliphatic chain, R3 is H, halo, OH, (cyclo)alkoxy, SH, (cyclo)alkylthio, CN, or an optionally substituted, (hetero)cycloaliph., (hetero)polycycloaliph., or (hetero)aromatic group; or two Rx are joined together to form an optionally-substituted spiro-linked (hetero)cycloaliph. group] were prepared as selective inhibitors of α4 integrins such as α4β1 and are of use in modulating cell adhesion for the prophylaxis or treatment of inflammatory diseases or disorders, such as rheumatoid arthritis, in which the extravasculation of leukocytes plays a role. Thus, Me 3-[1-(3,5-dichloroisonicotinoyl)-2,3-dihydro-1H-indol-5-yl]-2-[(3-oxospiro[3.5]non-1-en-1-yl)amino]propanoate was prepared by condensing Me 2-amino-3-[1-(3,5-dichloroisonicotinoyl)-2,3-dihydro-1H-indol-5-yl]propanoate (preparation given) with spiro[3.5]nonane-1,3-dione. Compds. of the examples generally have IC50 values in the α4β1 and α4β7 assays of ≤ 1 and ≤ 5 μM, resp. IC50 values for α integrins of other subgroups were 50 μM, thus demonstrating the potency and selectivity of compds. of the infection against α4 integrins.

IT **494227-85-9P 494227-86-0P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of bicyclic heteroarom. alanines as α4-integrin inhibitors)

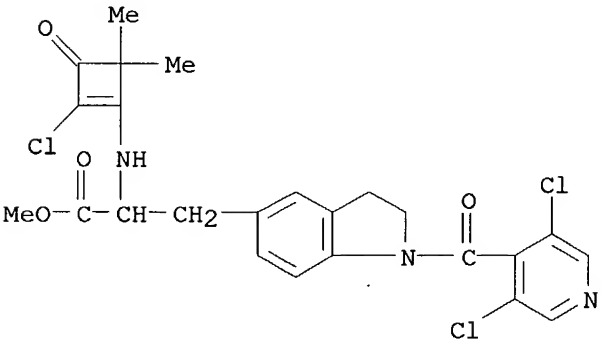
RN 494227-85-9 CAPLUS

CN 1H-Indole-5-propanoic acid, 1-[(3,5-dichloro-4-pyridinyl)carbonyl]-α-[(4,4-dimethyl-3-oxo-1-cyclobuten-1-yl)amino]-2,3-dihydro-, methyl ester (9CI) (CA INDEX NAME)



RN 494227-86-0 CAPLUS

CN 1H-Indole-5-propanoic acid, α-[(2-chloro-4,4-dimethyl-3-oxo-1-cyclobuten-1-yl)amino]-1-[(3,5-dichloro-4-pyridinyl)carbonyl]-2,3-dihydro-, methyl ester (9CI) (CA INDEX NAME)



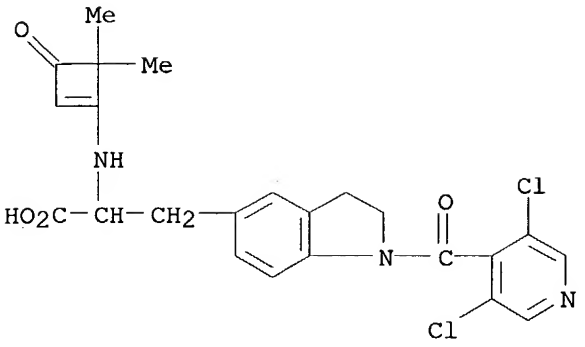
IT **494227-87-1P 494227-88-2P**

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

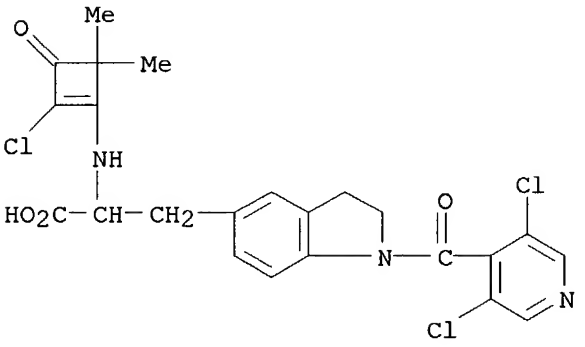
(preparation of bicyclic heteroarom. alanines as α4-integrin inhibitors)

RN 494227-87-1 CAPLUS

CN 1H-Indole-5-propanoic acid, 1-[(3,5-dichloro-4-pyridinyl)carbonyl]-α-[(4,4-dimethyl-3-oxo-1-cyclobuten-1-yl)amino]-2,3-dihydro- (9CI) (CA INDEX NAME)



RN 494227-88-2 CAPLUS
CN 1H-Indole-5-propanoic acid, α-[(2-chloro-4,4-dimethyl-3-oxo-1-cyclobuten-1-yl)amino]-1-[(3,5-dichloro-4-pyridinyl)carbonyl]-2,3-dihydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:675997 CAPLUS
DOCUMENT NUMBER: 137:217241
TITLE: Preparation of phenylalanine enamide derivatives possessing a cyclobutene group for use as integrin inhibitors
INVENTOR(S): Bailey, Stuart; Brown, Julien Alistair; Brand, Stephen; Johnson, James Andrew; Porter, John Robert; Head, John Clifford
PATENT ASSIGNEE(S): Celltech R & D Limited, UK
SOURCE: PCT Int. Appl., 201 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002068393	A1	20020906	WO 2002-GB206	20020118

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

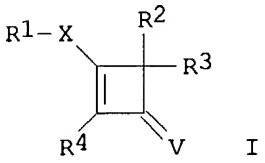
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

GB 2387845	A1	20031029	GB 2003-18429	20020118
EP 1370531	A1	20031217	EP 2002-715515	20020118
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2002007166	A	20040210	BR 2002-7166	20020118
US 2002169336	A1	20021114	US 2002-81072	20020222
NO 2003003710	A	20031022	NO 2003-3710	20030820

PRIORITY APPLN. INFO.: GB 2001-4418 A 20010222
GB 2001-14000 A 20010608
GB 2001-27562 A 20011116
WO 2002-GB206 W 20020118

OTHER SOURCE(S): MARPAT 137:217241

GI



I

AB Phenylalanine enamide derivs. I [R1 is a group Ar1-L2-Ar2-Alk- in which Ar1 is an optionally substituted (hetero)aromatic group, L2 is a covalent bond or a linker atom or group, Ar2 is an optionally substituted (hetero)arylene group, and Alk is CH2CHCO2H, CH:CCO2H, or CHCH2CO2H or a derivative or biostere; X = O, S, NH or alkylimino; V = O or S; R2, R3, R4 = L1-(Alk1)n(R5)v, in which L1 is a covalent bond or a linker atom or group, Alk1 is an optionally substituted (hetero)aliphatic chain, R5 = H, halo, OH, SH, CN, (un)substituted (cyclo)alkoxy, (cyclo)alkylthio, (hetero)(poly)cycloaliph. or (hetero)aromatic group; n = 0 or 1, and v = 1-3] were prepared Compds. I inhibit the binding of integrins to their ligands and are of use in the prophylaxis and treatment of immuno or inflammatory disorders or disorders involving the inappropriate growth or migration of cells. Thus, (2S)-2-[(3-oxospiro[3.5]non-1-en-1-yl)amino]-3-[4-[(3,5-dichloroisonicotinoyl)amino]phenyl]propanoic acid (claimed compound) was prepared by reaction of Et (2S)-2-amino-3-[4-[(3,5-dichloroisonicotinoyl)amino]phenyl]propanoate (preparation given) with 1-keto-3-hydroxyspiro[3.5]non-2-ene, followed by hydrolysis.

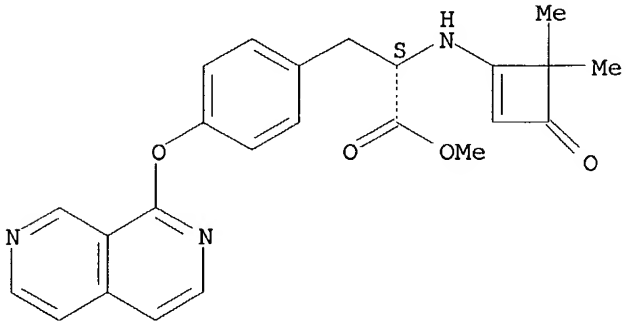
IT **455262-06-3P 455262-09-6P 455262-11-0P**
455262-13-2P 455262-15-4P 455262-17-6P
455262-20-1P 455262-22-3P 455262-24-5P
455262-26-7P 455262-30-3P 455262-32-5P
455262-34-7P 455262-43-8P 455262-60-9P
455262-67-6P 455262-75-6P 455262-76-7P
455263-04-4P 455263-09-9P 455263-42-0P
455263-46-4P 455263-48-6P 455263-52-2P
455263-71-5P 455263-73-7P 455263-75-9P
455263-91-9P 455263-96-4P 455264-08-1P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of phenylalanine enamide derivs. possessing a cyclobutene group for use as integrin inhibitors)

RN 455262-06-3 CAPLUS

CN L-Tyrosine, N-(4,4-dimethyl-3-oxo-1-cyclobuten-1-yl)-O-2,7-naphthyridin-1-yl-, methyl ester (9CI) (CA INDEX NAME)

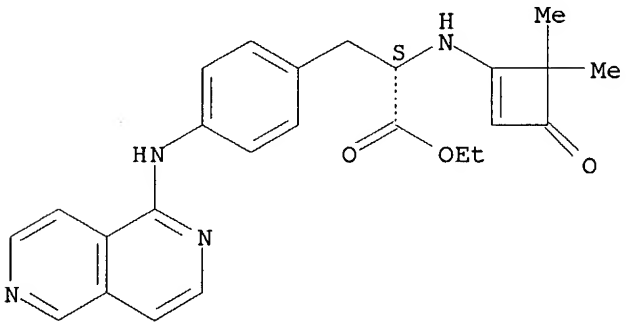
Absolute stereochemistry.



RN 455262-09-6 CAPLUS

CN L-Phenylalanine, N-(4,4-dimethyl-3-oxo-1-cyclobuten-1-yl)-4-(2,6-naphthyridin-1-ylamino)-, ethyl ester (9CI) (CA INDEX NAME)

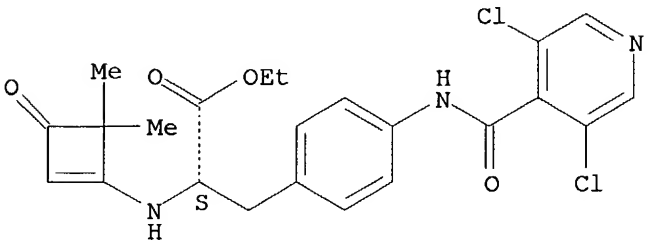
Absolute stereochemistry.



RN 455262-11-0 CAPLUS

CN L-Phenylalanine, 4-[[(3,5-dichloro-4-pyridinyl)carbonyl]amino]-N-(4,4-dimethyl-3-oxo-1-cyclobuten-1-yl)-, ethyl ester (9CI) (CA INDEX NAME)

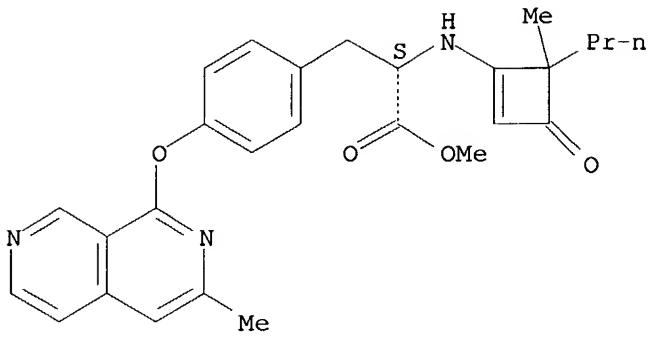
Absolute stereochemistry.



RN 455262-13-2 CAPLUS

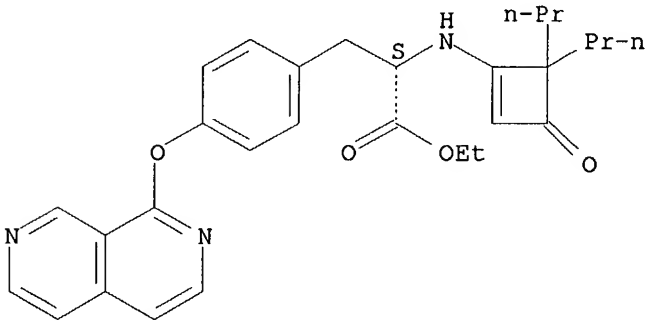
CN L-Tyrosine, O-(3-methyl-2,7-naphthyridin-1-yl)-N-(4-methyl-3-oxo-4-propyl-1-cyclobuten-1-yl)-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



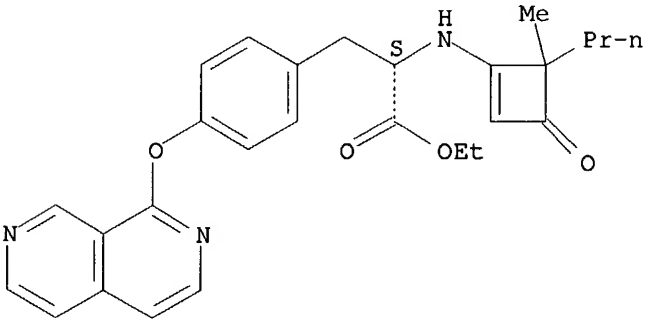
RN 455262-15-4 CAPLUS
CN L-Tyrosine, O-2,7-naphthyridin-1-yl-N-(3-oxo-4,4-dipropyl-1-cyclobuten-1-yl)-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



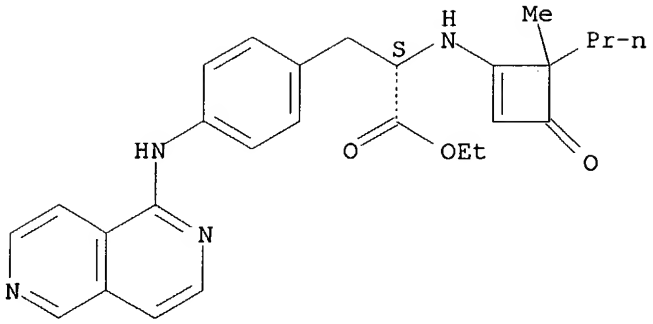
RN 455262-17-6 CAPLUS
CN L-Tyrosine, N-(4-methyl-3-oxo-4-propyl-1-cyclobuten-1-yl)-O-2,7-naphthyridin-1-yl-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



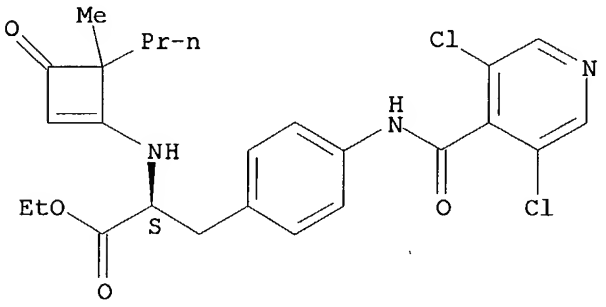
RN 455262-20-1 CAPLUS
CN L-Phenylalanine, N-(4-methyl-3-oxo-4-propyl-1-cyclobuten-1-yl)-4-(2,6-naphthyridin-1-ylamino)-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



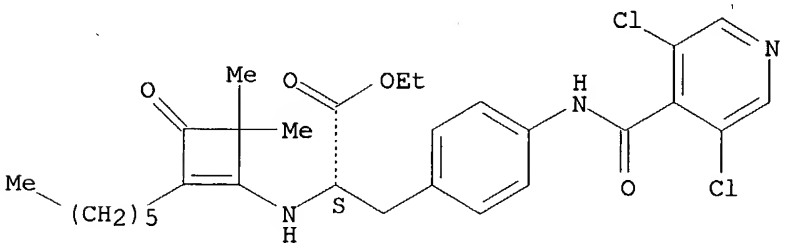
RN 455262-22-3 CAPLUS
CN L-Phenylalanine, 4-[[(3,5-dichloro-4-pyridinyl)carbonyl]amino]-N-(4-methyl-3-oxo-4-propyl-1-cyclobuten-1-yl)-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



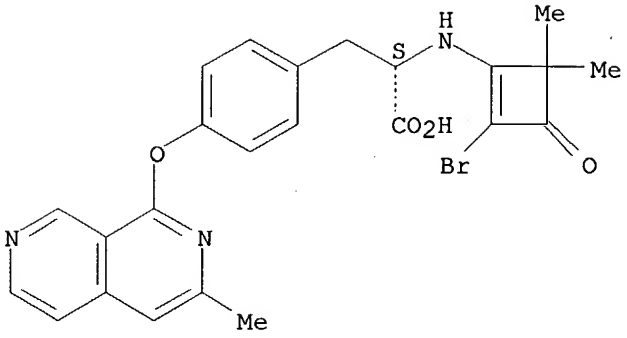
RN 455262-24-5 CAPLUS
CN L-Phenylalanine, 4-[[(3,5-dichloro-4-pyridinyl)carbonyl]amino]-N-(2-hexyl-4,4-dimethyl-3-oxo-1-cyclobuten-1-yl)-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 455262-26-7 CAPLUS
CN L-Tyrosine, N-(2-hexyl-4,4-dimethyl-3-oxo-1-cyclobuten-1-yl)-O-2,7-naphthyridin-1-yl-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

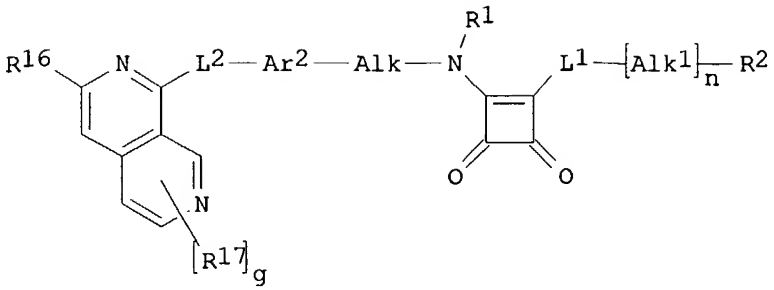


REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 5 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:408639 CAPLUS
DOCUMENT NUMBER: 136:401746
TITLE: Preparation of 3-substituted 2,7-naphthyridin-1-yl derivatives of squaric acid amides as selective α4 integrin inhibitors
INVENTOR(S): Head, John Clifford; McKay, Catherine; Porter, John Robert
PATENT ASSIGNEE(S): Celltech R & D Limited, UK
SOURCE: PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002042264	A1	20020530	WO 2001-GB5168	20011122
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002018400	A5	20020603	AU 2002-18400	20011122
EP 1337534	A1	20030827	EP 2001-997474	20011122
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2002137935	A1	20020926	US 2001-994411	20011127
US 6593338	B2	20030715		

PRIORITY APPLN. INFO.: GB 2000-28844 A 20001127
WO 2001-GB5168 W 20011122
OTHER SOURCE(S): MARPAT 136:401746
GI



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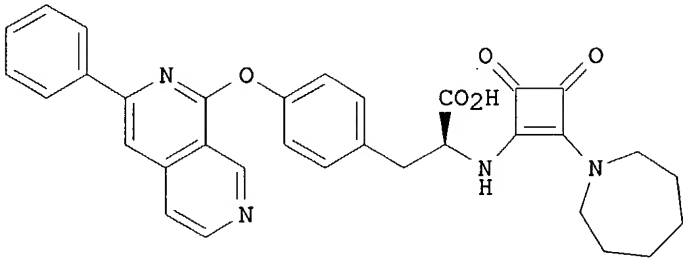


II

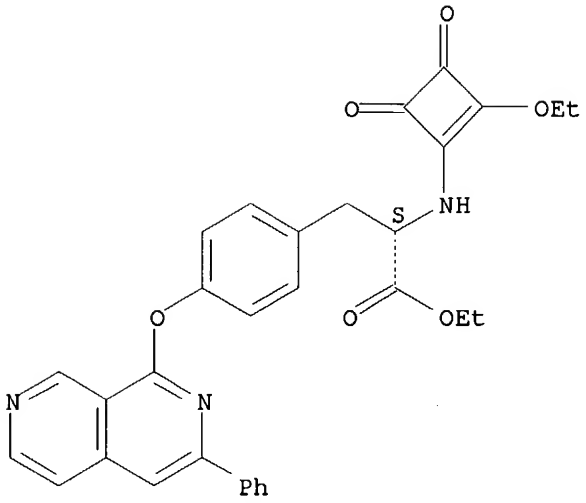
AB The title compds. [I; R1 = H, alkyl; L1, L2 = a covalent bond, a linker atom or group; Alk1 = (un)substituted aliphatic chain; n = 0-1; R2 = H; (un)substituted heteroaliph., cycloaliph., heterocycloaliph., polycycloaliph., heteropolycycloaliph., aromatic or heteroarom. group; Alk = CH2CHR, CH:CR; CH(CH2R), C(:CHR) (wherein R = CO2H or a derivative or biostere thereof); Ar2 = (un)substituted aromatic or heteroarom. linking group; R16 = L3(Alk2)tL4R20 (L3, L4 = a covalent bond, a linker atom or group; t = 0-1; Alk2 = (un)substituted aliphatic or heteroaliph. chain; R20 = (un)substituted aromatic or heteroarom. group); g = 0-4; R17 = H, halo, alkyl, etc.] which are able to inhibit the binding of integrins to their ligands and are of use in the prophylaxis and treatment of immune or inflammatory disorders or disorders involving the inappropriate growth or migration of cells, were prepared E.g., a multi-step synthesis of (S)-II was given. The exemplified compds. I showed IC50 of ≤ 1 μM in the α4β1 and α4β7 assays.

IT **431038-15-2P 431038-16-3P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of 3-substituted 2,7-naphthyridin-1-yl derivs. of squaric acid amides as selective α4 integrin inhibitors)

RN 431038-15-2 CAPLUS

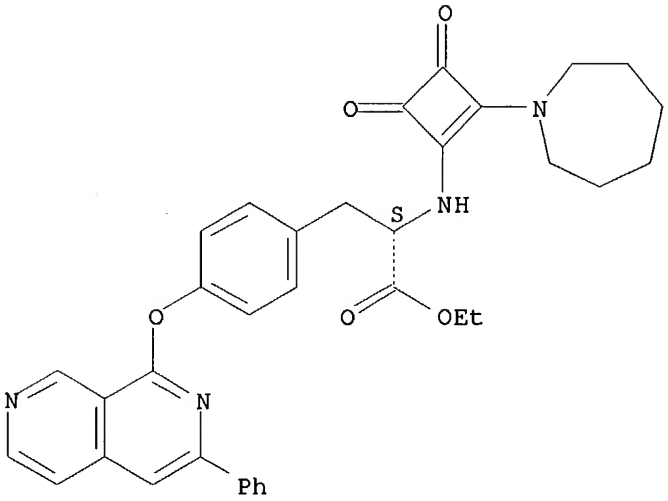
CN L-Tyrosine, N-(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-O-(3-phenyl-2,7-naphthyridin-1-yl)-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



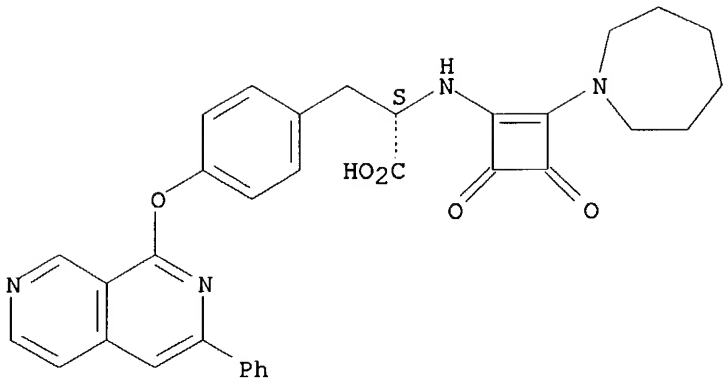
RN 431038-16-3 CAPLUS
CN L-Tyrosine, N-[2-(hexahydro-1H-azepin-1-yl)-3,4-dioxo-1-cyclobuten-1-yl]-O-(3-phenyl-2,7-naphthyridin-1-yl)-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **431038-17-4P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 3-substituted 2,7-naphthyridin-1-yl derivs. of squaric acid amides as selective α4 integrin inhibitors)
RN 431038-17-4 CAPLUS
CN L-Tyrosine, N-[2-(hexahydro-1H-azepin-1-yl)-3,4-dioxo-1-cyclobuten-1-yl]-O-(3-phenyl-2,7-naphthyridin-1-yl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:211229 CAPLUS
DOCUMENT NUMBER: 137:210402
TITLE: Squaric acid derivatives as VLA-4 integrin antagonists
AUTHOR(S): Porter, John R.; Archibald, Sarah C.; Childs, Kirstie; Critchley, David; Head, John C.; Linsley, Janeen M.; Parton, Ted A. H.; Robinson, Martyn K.; Shock, Anthony; Taylor, Richard J.; Warrellow, Graham J.; Alexander, Rikki P.; Langham, Barry
CORPORATE SOURCE: Celltech R&D Ltd., Slough, SL1 4EN, UK
SOURCE: Bioorganic & Medicinal Chemistry Letters (2002), 12(7), 1051-1054
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB SAR studies aimed at improving the rate of clearance by the incorporation of a 3,4-diamino-3-cyclobutene-1,2-dione group as an amino acid isostere in a series of VLA-4 integrin antagonists are described.

IT **312292-16-3P 312292-60-7P 312292-62-9P**
312292-64-1P 312292-66-3P 312293-18-8P
312293-32-6P 312293-42-8P 312293-43-9P
312293-44-0P 312293-49-5P 312293-50-8P
312293-56-4P 312293-57-5P 312293-58-6P
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312293-81-5P 312293-82-6P 312293-89-3P
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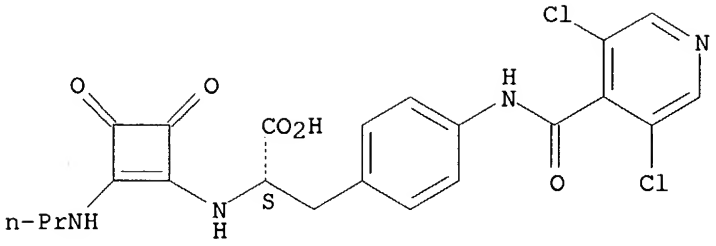
312294-01-2P 312294-02-3P 348113-48-4P
348113-50-8P 348113-52-0P 348113-54-2P
455894-84-5P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(squaric acid derivs. as VLA-4 integrin antagonists)

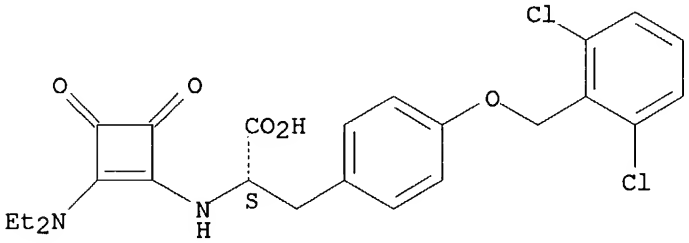
RN 312292-16-3 CAPLUS
CN L-Phenylalanine, 4-[[(3,5-dichloro-4-pyridinyl)carbonyl]amino]-N-[3,4-dioxo-2-(propylamino)-1-cyclobuten-1-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



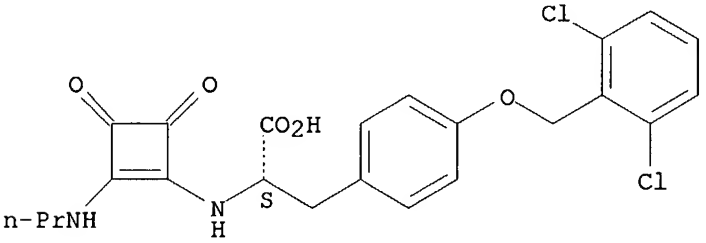
RN 312292-60-7 CAPLUS
CN L-Tyrosine, O-[(2,6-dichlorophenyl)methyl]-N-[2-(diethylamino)-3,4-dioxo-1-cyclobuten-1-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



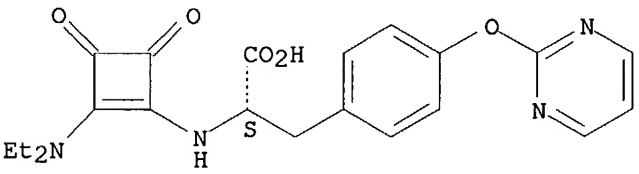
RN 312292-62-9 CAPLUS
CN L-Tyrosine, O-[(2,6-dichlorophenyl)methyl]-N-[3,4-dioxo-2-(propylamino)-1-cyclobuten-1-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 312292-64-1 CAPLUS
CN L-Tyrosine, N-[2-(diethylamino)-3,4-dioxo-1-cyclobuten-1-yl]-O-2-pyrimidinyl- (9CI) (CA INDEX NAME)

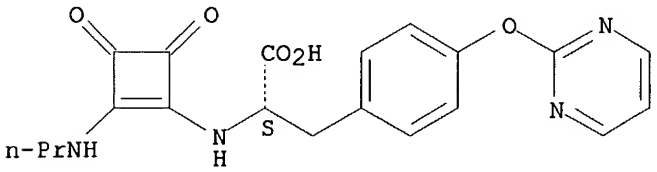
Absolute stereochemistry.



RN 312292-66-3 CAPLUS

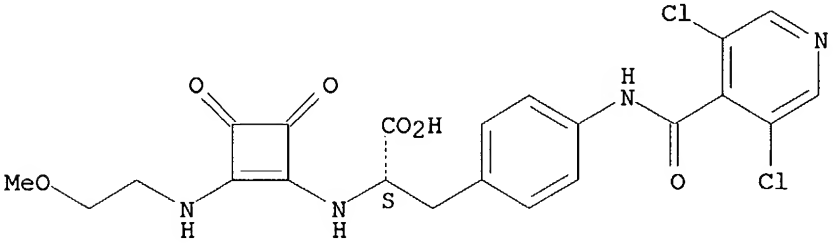
CN L-Tyrosine, N-[3,4-dioxo-2-(propylamino)-1-cyclobuten-1-yl]-O-2-pyrimidinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



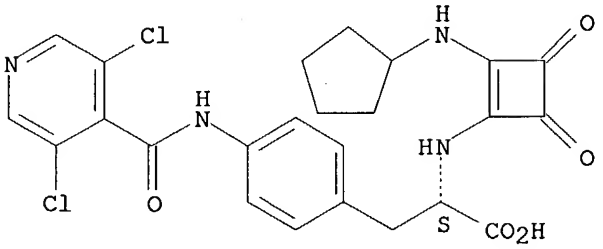
RN 312293-18-8 CAPLUS
CN L-Phenylalanine, 4-[[(3,5-dichloro-4-pyridinyl)carbonyl]amino]-N-[2-[(2-methoxyethyl)amino]-3,4-dioxo-1-cyclobuten-1-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 312293-32-6 CAPLUS
CN L-Phenylalanine, N-[2-(cyclopentylamino)-3,4-dioxo-1-cyclobuten-1-yl]-4-[[(3,5-dichloro-4-pyridinyl)carbonyl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

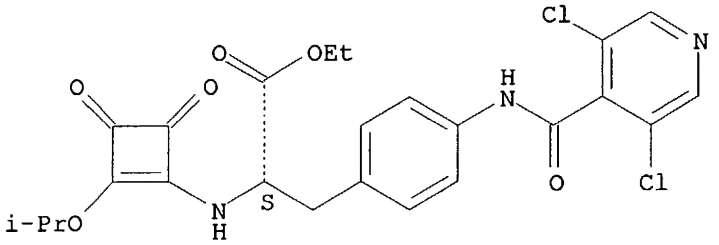


RN 312293-42-8 CAPLUS
CN L-Phenylalanine, 4-[[(3,5-dichloro-4-pyridinyl)carbonyl]amino]-N-[2-[(1-methylethyl)amino]-3,4-dioxo-1-cyclobuten-1-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

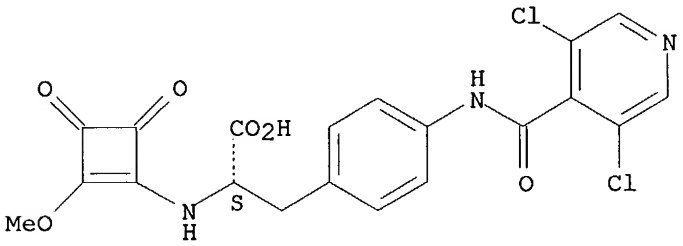
IT **312292-12-9P 312293-94-0DP,** resin-bound
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(squaric acid derivs. as VLA-4 integrin antagonists)
RN 312292-12-9 CAPLUS
CN L-Phenylalanine, 4-[[(3,5-dichloro-4-pyridinyl)carbonyl]amino]-N-[2-(1-methylethoxy)-3,4-dioxo-1-cyclobuten-1-yl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 312293-94-0 CAPLUS
CN L-Phenylalanine, 4-[[(3,5-dichloro-4-pyridinyl)carbonyl]amino]-N-(2-methoxy-3,4-dioxo-1-cyclobuten-1-yl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

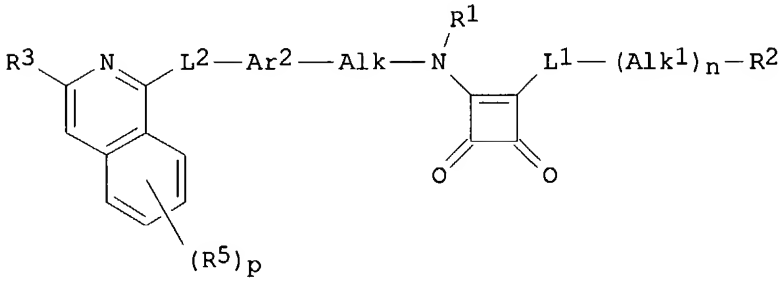


REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 7 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:107317 CAPLUS
DOCUMENT NUMBER: 136:167287
TITLE: Preparation of novel 3-substituted isoquinolin-1-yl derivatives of squaric acid amides as selective α4-integrin inhibitors
INVENTOR(S): Head, John Clifford; Porter, John Robert; McKay, Catherine
PATENT ASSIGNEE(S): Celltech R & D Limited, UK
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2002010136 A1 20020207 WO 2001-GB3429 20010730
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
EP 1305291 A1 20030502 EP 2001-953234 20010730
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
JP 2004505110 T2 20040219 JP 2002-516268 20010730
US 6469025 B1 20021022 US 2001-920206 20010801
US 2002177605 A1 20021128
PRIORITY APPLN. INFO.: GB 2000-18969 A 20000802
GB 2000-28837 A 20001127
WO 2001-GB3429 W 20010730
OTHER SOURCE(S): MARPAT 136:167287
GI



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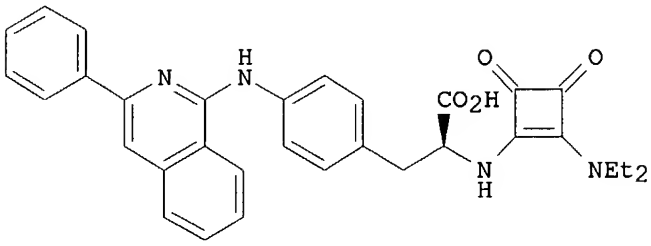


II

AB Squaric acid derivs. I are described [wherein: R1 = H or C1-6 alkyl; L1 = covalent bond or linker atom or group; Alk1 = (un)substituted aliphatic chain; n = 0 or 1; R2 = H or (un)substituted heteroaliph., (hetero)cycloaliph., (hetero)polycycloaliph., (hetero)aromatic; Alk = CH2CH(R), CH:C(R), CH(CH2R), C(:CHR); R = CO2H or derivative or biostere thereof; Ar2 = (un)substituted (hetero)aromatic linker; L2 = covalent bond or linker atom or group; R3 = L3(Alk2)mL4R4; L3, L4 = covalent bond or linker atom or group; m = 0 or 1; Alk2 = (un)substituted (hetero)aliphatic chain; R4 = (un)substituted (hetero)aromatic group; p = 0-5; R5 = H, halo, (un)substituted alkyl, alkoxy, (hetero)aromatic, SH, OH, (un)substituted NH2, etc.; including salts, solvates, hydrates, and N-oxides]. The compds. are

able to inhibit the binding of integrins to their ligands and are of use in the prophylaxis and treatment of immune or inflammatory disorders, or disorders including the inappropriate growth or migration of cells. In particular, the compds. are selective inhibitors of α4 integrins. Approx. 50 compds. I were prepared For instance, mono-amidation of the squarate diester 3,4-diisopropoxy-3-cyclobutene-1,2-dione with a corresponding amino acid ester (84%), followed by a second amidation with diethylamine (85%), and alkaline hydrolysis of the ester function (67%), gave title compound II. In bioassays against several integrins, the example compds. generally had IC50 values of ≤ 1 μM against α4β1 and α4β7 integrins, but IC50 ≥ 50 μM against α5β1, αmβ2, and αIIbβ3 integrins.

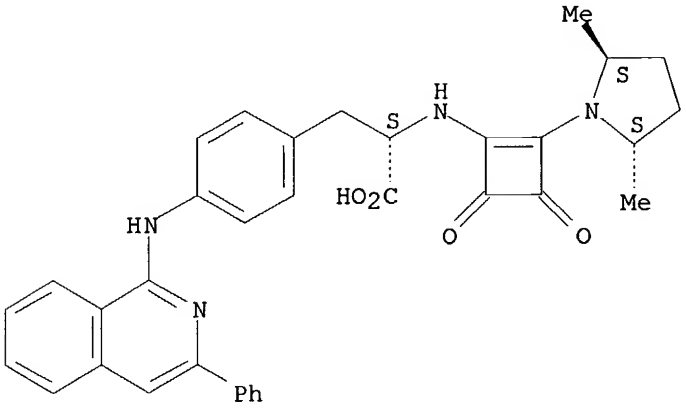
IT **395092-68-9P**, Ethyl (S)-2-[(2-isopropoxy-3,4-dioxocyclobuten-1-yl)amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoate **395092-70-3P**, Methyl (S)-2-[[2-(N,N-diethylamino)-3,4-dioxocyclobuten-1-yl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoate **395092-71-4P**, (S)-2-[[2-(N,N-Diethylamino)-3,4-dioxocyclobuten-1-yl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid **395092-73-6P**, Methyl (S)-2-[[2-(N,N-dipropylamino)-3,4-dioxocyclobuten-1-yl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoate **395092-75-8P**, (S)-2-[[2-(N,N-Dipropylamino)-3,4-dioxocyclobuten-1-yl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid **395092-77-0P**, Methyl (2S)-2-[[2-(2,5-dimethylpyrrolidin-1-yl)-3,4-dioxocyclobuten-1-yl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoate **395092-78-1P**, (2S)-2-[[2-(2,5-Dimethylpyrrolidin-1-yl)-3,4-dioxocyclobuten-1-yl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid **395092-79-2P**, Ethyl (S)-2-[(2-isopropoxy-3,4-dioxocyclobuten-1-yl)amino]-3-[4-[[3-(4-fluorophenyl)-1-isoquinolinyl]amino]phenyl]propionate **395092-81-6P**, Ethyl (2S)-2-[[2-(2,5-dimethylpyrrolidin-1-yl)-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[[3-(4-fluorophenyl)isoquinolin-1-yl]amino]phenyl]propanoate **395092-82-7P**, (2S)-2-[[2-(2,5-Dimethylpyrrolidin-1-yl)-3,4-dioxocyclobuten-1-yl]amino]-3-[4-[[3-(4-fluorophenyl)isoquinolin-1-yl]amino]phenyl]propanoic acid **395092-83-8P**, Ethyl (2S)-2-[[2-(2-methylpiperidin-1-yl)-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[[3-(4-fluorophenyl)isoquinolin-1-yl]amino]phenyl]propanoate **395092-84-9P**, (2S)-2-[[2-(2-Methylpiperidin-1-yl)-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[[3-(4-fluorophenyl)isoquinolin-1-yl]amino]phenyl]propanoic acid **395092-86-1P**, (2S)-3-[4-(3-Phenyl-1-isoquinolinylamino)phenyl]-2-(2-morpholino-3,4-dioxocyclobut-1-enylamino)propanoic acid **395092-87-2P**, (2S)-2-[[2-(Isobutylamino)-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid **395092-88-3P**, (2S)-2-[[2-[(2-Methoxyethyl)amino]-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid **395092-89-4P**, (2S)-2-[[2-(2-Ethylpiperidin-1-yl)-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid **395092-90-7P**, (2S)-2-[[2-(2-Propylpiperidin-1-yl)-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid **395092-91-8P**, (2S)-2-[[2-(5-Ethyl-2-methylpiperidin-1-yl)-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid **395092-92-9P**, (2S)-2-[[2-[(2R,5R)-2,5-Bis(methoxymethyl)pyrrolidin-1-yl]-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid **395092-93-0P**, (2S)-2-[[2-(Propylamino)-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid **395092-94-1P**, (S)-3-[4-[(3-Phenyl-1-isoquinolinyl)amino]phenyl]-2-[[2-(N-isopropyl-N-ethylamino)-3,4-dioxocyclobut-1-enyl]amino]propanoic acid

395092-95-2P, (2S)-2-[[2-(Diisobutylamino)-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid **395092-96-3P**, (2S)-2-[[2-[(2R)-2-(Methoxymethyl)pyrrolidin-1-yl]-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid **395092-98-5P**, (S)-3-[4-[(3-Phenyl-1-isoquinolinyl)amino]phenyl]-2-[[2-(N-cyclohexyl-N-ethylamino)-3,4-dioxocyclobut-1-enyl]amino]propanoic acid **395092-99-6P**, (2S)-2-[[2-(Piperidin-1-yl)-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid **395093-00-2P**, (2S)-2-[[2-[2,5-Bis(2-methoxyethyl)amino]-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid **395093-01-3P**, (2S)-2-[[2-(3-Methylpiperidin-1-yl)-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid **395093-02-4P**, (2S)-2-[[2-(Dibutylamino)-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid **395093-03-5P**, (2S)-2-[[2-[2-(Pyridin-3-yl)pyrrolidin-1-yl]-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid **395093-04-6P**, (2S)-2-[[2-[Ethyl(pyridin-4-ylmethyl)amino]-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid **395093-05-7P 395093-07-9P**, (2S)-2-[[2-(Decahydroquinolin-1-yl)-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid **395093-08-0P**, (2S)-2-[[2-[Methyl[(αS)-α-methylbenzyl]amino]-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid **395093-10-4P**, (S)-3-[4-[(3-Phenyl-1-isoquinolinyl)amino]phenyl]-2-[(2-(azepan-1-yl)-3,4-dioxocyclobut-1-enyl)amino]propanoic acid **395093-11-5P**, (2S)-2-[[2-(Thiomorpholin-4-yl)-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid **395093-12-6P**, (2S)-2-[[2-(2,6-Dimethylmorpholin-4-yl)-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid **395093-13-7P**, (2S)-2-[[2-(Cyclopropylamino)-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid **395093-16-0P**, (S)-3-[4-[(3-Phenyl-1-isoquinolinyl)amino]phenyl]-2-[[2-(N-cyclopropylmethyl-N-propylamino)-3,4-dioxocyclobut-1-enyl]amino]propanoic acid **395093-17-1P**, (2S)-2-[[2-(Isopropylamino)-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid **395093-18-2P**, (2S)-2-[[2-(1,2,3,4-Tetrahydroisoquinolin-2-yl)-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid **395093-19-3P**, (2S)-2-[[2-(N-Benzyl-N-isopropylamino)-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid **395093-21-7P**, (2S)-2-[[2-(4-Methylhomopiperazin-1-yl)-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid **395093-23-9P**, (2S)-2-[[2-[4-(tert-Butoxycarbonyl)homopiperazin-1-yl]-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid **395093-24-0P**, (2S)-2-[[2-(Thiazolidin-3-yl)-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid **395093-25-1P**, (2S)-2-[[2-(N-Benzyl-N-ethylamino)-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid **395093-26-2P**, (2S)-2-[[2-[(2S,5S)-2,5-Dimethylpyrrolidin-1-yl]-3,4-dioxocyclobut-1-enyl]amino]-3-[4-[(3-phenyl-1-isoquinolinyl)amino]phenyl]propanoic acid

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

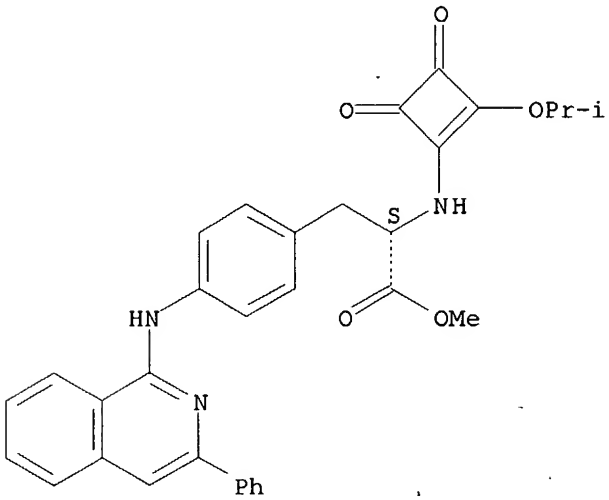
RN 395093-26-2 CAPLUS
CN L-Phenylalanine, N-[2-[(2S,5S)-2,5-dimethyl-1-pyrrolidinyl]-3,4-dioxo-1-cyclobuten-1-yl]-4-[(3-phenyl-1-isoquinolinyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **395093-29-5**, Methyl (S)-3-[4-(3-phenyl-1-isoquinolinylamino)phenyl]-2-(2-isopropoxy-3,4-dioxocyclobut-1-enylamino)propanoate
RL: RCT (Reactant); RACT (Reactant or reagent)
(precursor; preparation of 3-substituted isoquinolin-1-yl derivs. of squaric acid amides as α4-integrin inhibitors)
RN 395093-29-5 CAPLUS
CN L-Phenylalanine, N-[2-(1-methylethoxy)-3,4-dioxo-1-cyclobuten-1-yl]-4-[(3-phenyl-1-isoquinolinyl)amino]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 8 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:51439 CAPLUS

DOCUMENT NUMBER: 136:118460
TITLE: Preparation of squaric acid derivatives containing a bicyclic heteroaromatic ring as integrin antagonists
INVENTOR(S): Langham, Barry John; Alexander, Rikki Peter; Head, John Clifford; Linsley, Janeen Marsha; Porter, John Robert; Archibald, Sarah Catherine; Warrellow, Graham John
PATENT ASSIGNEE(S): Celltech R & D Limited, UK
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002004426	A1	20020117	WO 2001-GB3028	20010705
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
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US 6740654	B2	20040525		
EP 1301488	A1	20030416	EP 2001-945540	20010705
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JP 2004502762	T2	20040129	JP 2002-509293	20010705

PRIORITY APPLN. INFO.:
GB 2000-16785 A 20000707
GB 2000-28364 A 20001121
WO 2001-GB3028 W 20010705

OTHER SOURCE(S): MARPAT 136:118460
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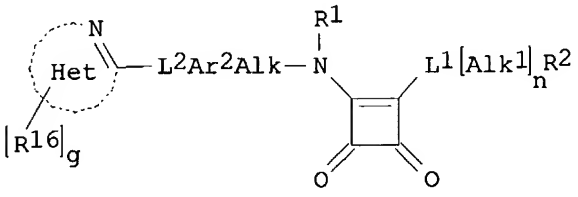

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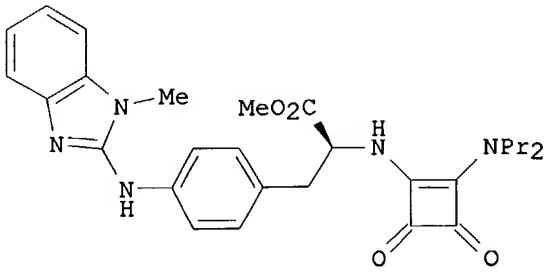


II

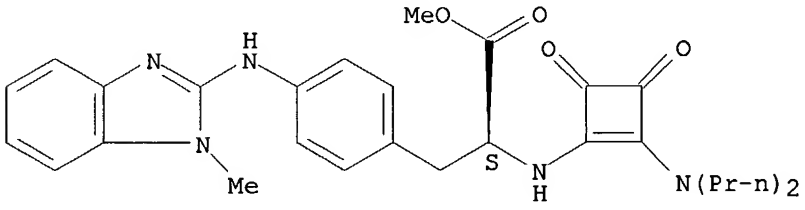
AB The title compds. [I; Het = (un)substituted bicyclic fused ring heteroarom. group; R16 = H, alkyl, etc.; g = 0-4; L2 = a bond, O, S, CO, etc.; Ar2 = (un)substituted (hetero)aromatic; Alk = CH2CHR, CH:CR, CH(CH2R), C(:CHR) (wherein R = CO2H or a derivative or biostere thereof); R1 = H, alkyl; L1 = a covalent bond, a linker atom or group; Alk1 = (un)substituted aliphatic chain; n = 0-1; R2 = H, (un)substituted heteroaliph., cycloaliph., heterocycloaliph., polycycloalphatic, heteropolycycloaliph., aromatic or heteroarom. group other than a 2,6-naphthyridin-1-yl, isoquinolin-1-yl, 2,7-naphthyridin-1-yl or quinazolin-4-yl] which are able to inhibit the binding of integrins to their ligands and are of use in the prophylaxis and treatment of immune or inflammatory disorders, or disorders involving the inappropriate growth or migration of cells, were prepared Thus, reacting Et (S)-2-amino-3-{4-[(1-methylbenzimidazol-2-yl)amino]phenyl}propanoate.CF3CO2H with diisopropylsquarate in the presence of DIPEA in iso-Pr followed by treatment of the resulting Et (S)-2-{[2-(isopropoxy)-3,4-dioxo-1-cyclobutenyl]amino}-3-{4-[(1-methylbenzimidazol-2-yl)amino]phenyl}propanoate with dipropylamine in MeOH afforded II. The exemplified compds. I showed IC50 of ≤ 1 μM in the α4β1 and α4β7 assays.

IT **389637-00-7P 389637-01-8P 389637-02-9P**
389637-06-3P 389637-07-4P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of squaric acid derivs. containing a bicyclic heteroarom. ring as
integrin antagonists)

RN 389637-00-7 CAPLUS

CN L-Phenylalanine, N-[2-(dipropylamino)-3,4-dioxo-1-cyclobuten-1-yl]-4-[(1-methyl-1H-benzimidazol-2-yl)amino]-, methyl ester (9CI) (CA INDEX NAME)

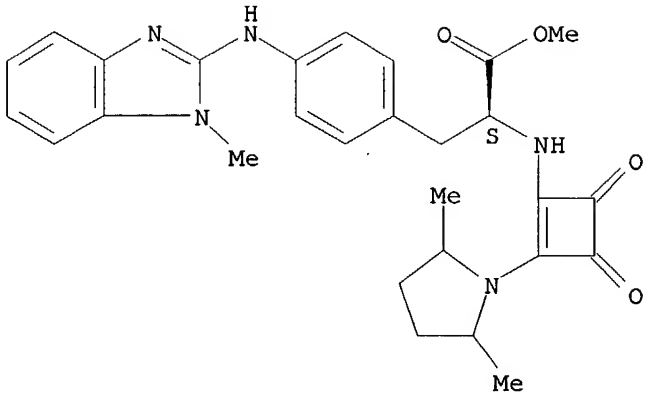
Absolute stereochemistry.



RN 389637-01-8 CAPLUS

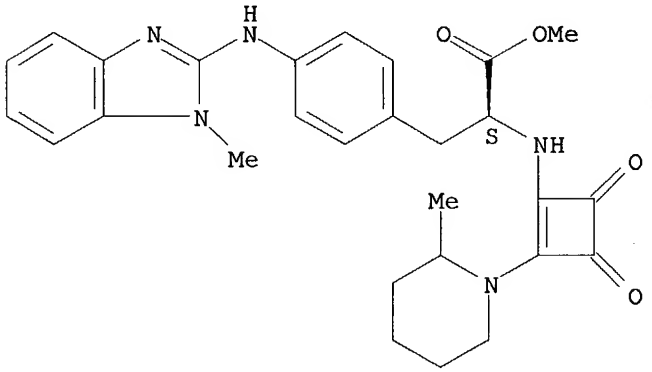
CN L-Phenylalanine, N-[2-(2,5-dimethyl-1-pyrrolidinyl)-3,4-dioxo-1-cyclobuten-1-yl]-4-[(1-methyl-1H-benzimidazol-2-yl)amino]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



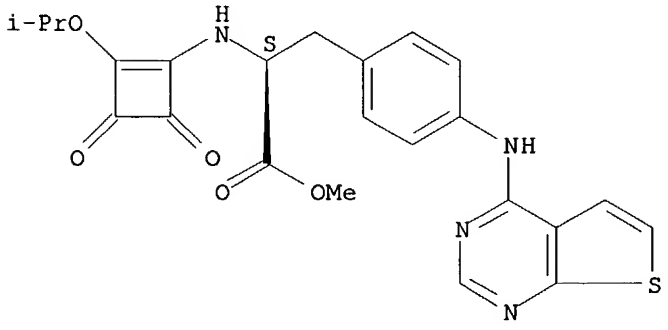
RN 389637-02-9 CAPLUS
CN L-Phenylalanine, 4-[(1-methyl-1H-benzimidazol-2-yl)amino]-N-[2-(2-methyl-1-piperidinyl)-3,4-dioxo-1-cyclobuten-1-yl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 389637-06-3 CAPLUS
CN L-Phenylalanine, N-[2-(1-methylethoxy)-3,4-dioxo-1-cyclobuten-1-yl]-4-(thieno[2,3-d]pyrimidin-4-ylamino)-, methyl ester (9CI) (CA INDEX NAME)

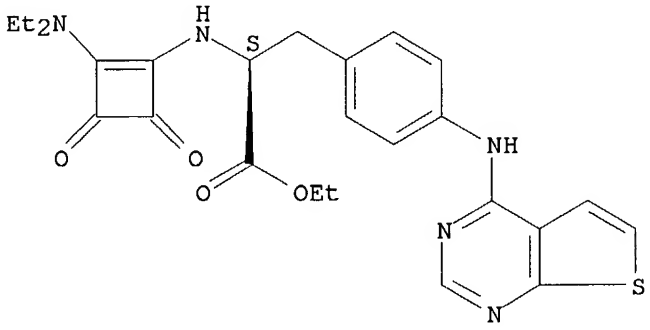
Absolute stereochemistry.



RN 389637-07-4 CAPLUS
CN L-Phenylalanine, N-[2-(diethylamino)-3,4-dioxo-1-cyclobuten-1-yl]-4-

(thieno[2,3-d]pyrimidin-4-ylamino)-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

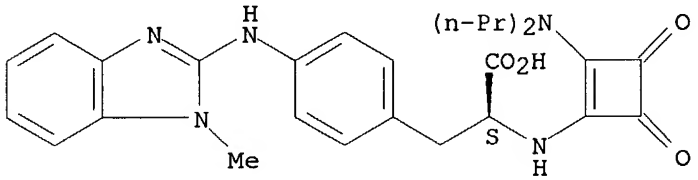


IT **389637-03-0P 389637-04-1P 389637-05-2P**
389637-08-5P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of squaric acid derivs. containing a bicyclic heteroarom. ring as
integrin antagonists)

RN 389637-03-0 CAPLUS

CN L-Phenylalanine, N-[2-(dipropylamino)-3,4-dioxo-1-cyclobuten-1-yl]-4-[(1-methyl-1H-benzimidazol-2-yl)amino]- (9CI) (CA INDEX NAME)

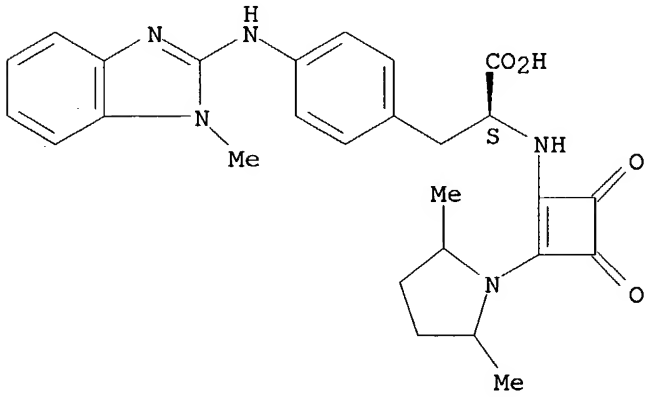
Absolute stereochemistry.



RN 389637-04-1 CAPLUS

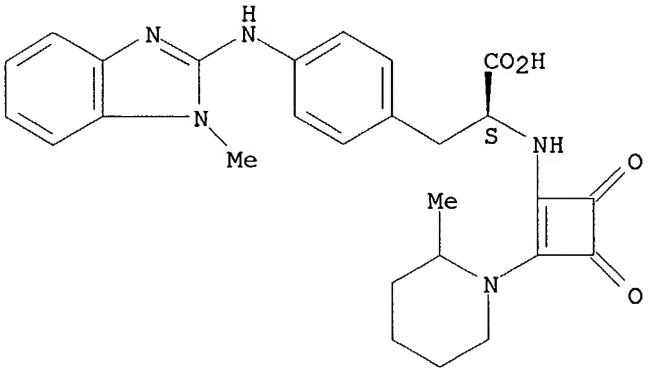
CN L-Phenylalanine, N-[2-(2,5-dimethyl-1-pyrrolidinyl)-3,4-dioxo-1-cyclobuten-1-yl]-4-[(1-methyl-1H-benzimidazol-2-yl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



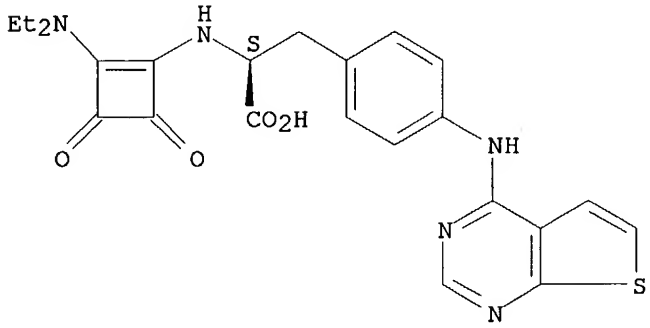
RN 389637-05-2 CAPLUS
CN L-Phenylalanine, 4-[(1-methyl-1H-benzimidazol-2-yl)amino]-N-[2-(2-methyl-1-piperidinyl)-3,4-dioxo-1-cyclobuten-1-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



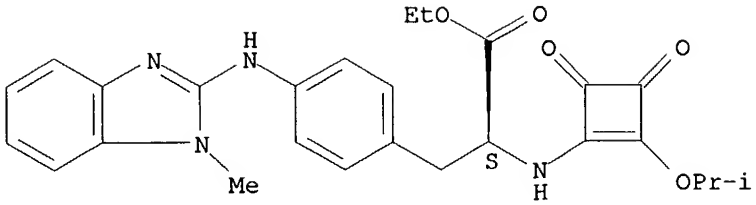
RN 389637-08-5 CAPLUS
CN L-Phenylalanine, N-[2-(diethylamino)-3,4-dioxo-1-cyclobuten-1-yl]-4-(thieno[2,3-d]pyrimidin-4-ylamino)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **389637-11-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of squaric acid derivs. containing a bicyclic heteroarom. ring as
integrin antagonists)
RN 389637-11-0 CAPLUS
CN L-Phenylalanine, 4-[(1-methyl-1H-benzimidazol-2-yl)amino]-N-[2-(1-methylethoxy)-3,4-dioxo-1-cyclobuten-1-yl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



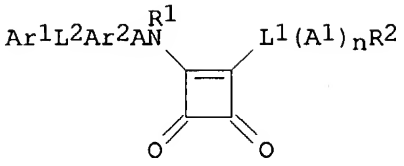
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 9 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:886114 CAPLUS
DOCUMENT NUMBER: 136:20059
TITLE: Preparation of naphthyridine squaric acid derivatives as integrin inhibitors.
INVENTOR(S): Langham, Barry John; Alexander, Rikki Peter; Head, John Clifford; Linsley, Janeen Marsha; Porter, John Robert; Archibald, Sarah Catherine; Warrellow, Graham John
PATENT ASSIGNEE(S): Celltech R & D Limited, UK
SOURCE: PCT Int. Appl., 101 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001092256	A1	20011206	WO 2001-GB2425	20010530
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002115684	A1	20020822	US 2001-867016	20010529
US 6545013	B2	20030408		
EP 1286995	A1	20030305	EP 2001-934177	20010530
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003535088	T2	20031125	JP 2002-500869	20010530

PRIORITY APPLN. INFO.:
GB 2000-13101 A 20000530
GB 2000-28841 A 20001127
WO 2001-GB2425 W 20010530

OTHER SOURCE(S): MARPAT 136:20059
GI



I

AB Title compds. [I; Ar1 = (substituted) 2,7-naphthridin-1-yl; L2 = bond, linker atom or group; Ar2 = (substituted) aromatic or heteroarom. chain; A = CH2CHR, CH:CR, CHCH2R, C:CHR; R = CO2H or a derivative or biostere thereof; R1 = H, alkyl; L1 = bond, linker atom or group; A1 = (substituted) aliphatic chain; n = 0, 1; R2 = H, (substituted) heteroaliph., cycloaliph., heterocycloaliph., polycycloaliph., heteropolycycloaliph., aryl, heteroaryl] and the salts, solvates, hydrates and N-oxides thereof, were prepared Thus, a mixture of 1,2-diisopropoxy-3,4-dioxocyclobut-1-ene and Et (S)-3-[4-(2,7-naphthyridin-1-ylamino)phenyl]-2-aminopropanoate (preparation given) in EtOH was stirred at 50° overnight to give 79% Et (S)-3-[4-(2,7-naphthyridin-1-ylamino)phenyl]-2-(2-isopropoxy-3,4-dioxocyclobut-1-enylamino)propanoate. Tested I in α4β1 and α4β7 screens inhibited cell adhesion with IC50 ≤1 μM.

IT **378251-41-3P 378251-42-4P 378251-43-5P**
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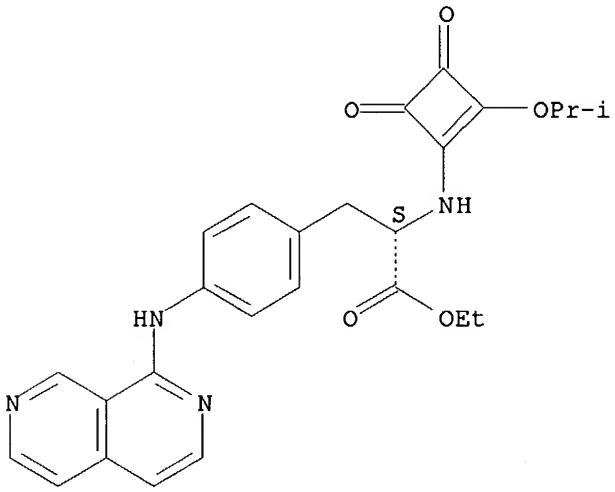
378252-77-8P 378252-78-9P 378252-79-0P
378252-80-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of naphthyridine squaric acid derivs. as integrin inhibitors)

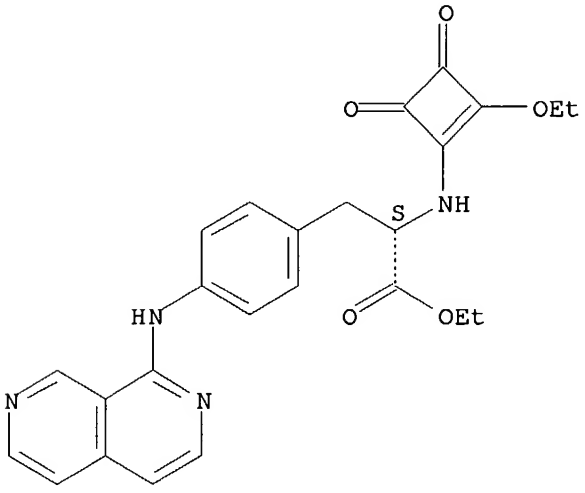
RN 378251-41-3 CAPLUS
CN L-Phenylalanine, N-[2-(1-methylethoxy)-3,4-dioxo-1-cyclobuten-1-yl]-4-(2,7-naphthyridin-1-ylamino)-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 378251-42-4 CAPLUS
CN L-Phenylalanine, N-(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-4-(2,7-naphthyridin-1-ylamino)-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



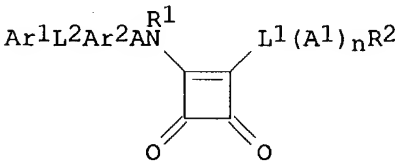
RN 378251-43-5 CAPLUS
CN L-Phenylalanine, N-[2-(diethylamino)-3,4-dioxo-1-cyclobuten-1-yl]-4-(2,7-

L14 ANSWER 10 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:886077 CAPLUS
DOCUMENT NUMBER: 136:20029
TITLE: Preparation of squaric acid isoquinoline derivatives as integrin binding inhibitors.
INVENTOR(S): Langham, Barry John; Alexander, Rikki Peter; Head, John Clifford; Linsley, Janeen Marsha; Porter, John Robert; Archibald, Sarah Catherine; Warrelow, Graham John
PATENT ASSIGNEE(S): Celltech R & D Limited, UK
SOURCE: PCT Int. Appl., 102 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001092233	A1	20011206	WO 2001-GB2390	20010530
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6403608	B1	20020611	US 2001-867060	20010529
EP 1284967	A1	20030226	EP 2001-934158	20010530
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003535081	T2	20031125	JP 2002-500847	20010530

PRIORITY APPLN. INFO.:
GB 2000-13087 A 20000530
GB 2000-19060 A 20000803
GB 2000-28842 A 20001127
WO 2001-GB2390 W 20010530

OTHER SOURCE(S): MARPAT 136:20029
GI



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AB Title compds. [I; Ar1 = 3-substituted isoquinolin-1-yl; L1, L2 = bond, linker atom or group; Ar2 = (substituted) aromatic or heteroanomatic chain; A = CH2CHR, CH:CR, CH(CH2R), C(:CHR); R = CO2H or a derivative or biostere thereof; R1 = H, alkyl; A1 = (substituted) aliphatic chain; n = 0, 1; R2 = H, (substituted) heteroaliph., cycloaliph., heterocycloaliph., polycycloaliph., heteropolycycloalkyl], were prepared as integrin binding inhibitors (no data). Thus, Me (S)-2-amino-3-[4-(3-ethyl-1-isoquinolinylamino)phenyl]propanoate (preparation given), 3,4-diisopropoxy-3-

cyclobuten-1,2-dione, and diisopropylethylamine were stirred 16 h in MeOH to give 100% Me (S)-3-[4-(3-ethyl-1-isoquinolinylamino)phenyl]-2-[(2-isopropoxy-3,4-dioxocyclobut-1-enyl)amino]propanoate. I generally show IC50 ≤1 μM in integrin α4β1 and α4β7 cell adhesion inhibition assays.

IT **378234-59-4P 378234-60-7P 378234-61-8P**
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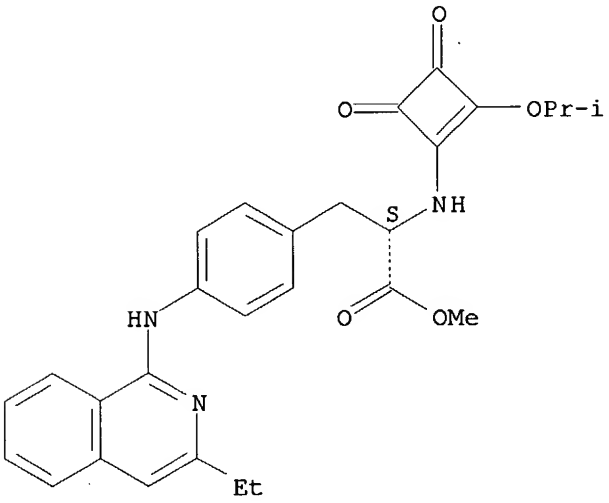
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of squaric acid isoquinoline derivs. as integrin binding inhibitors)

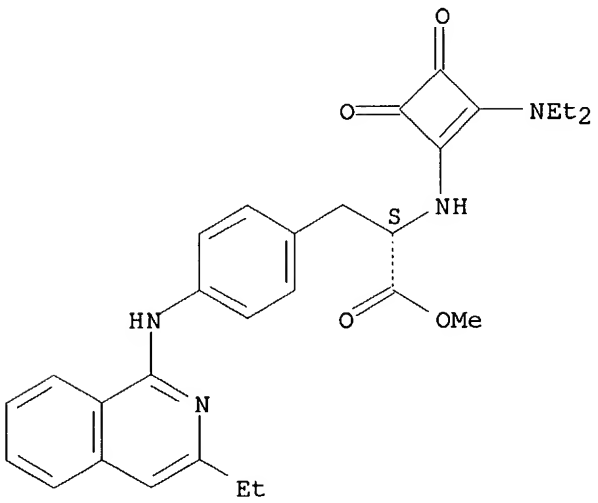
RN 378234-59-4 CAPLUS
CN L-Phenylalanine, 4-[(3-ethyl-1-isoquinolinyl)amino]-N-[2-(1-methylethoxy)-3,4-dioxo-1-cyclobuten-1-yl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



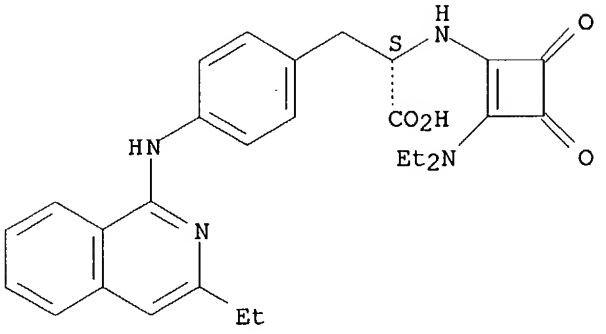
RN 378234-60-7 CAPLUS
CN L-Phenylalanine, N-[2-(diethylamino)-3,4-dioxo-1-cyclobuten-1-yl]-4-[(3-ethyl-1-isoquinolinyl)amino]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



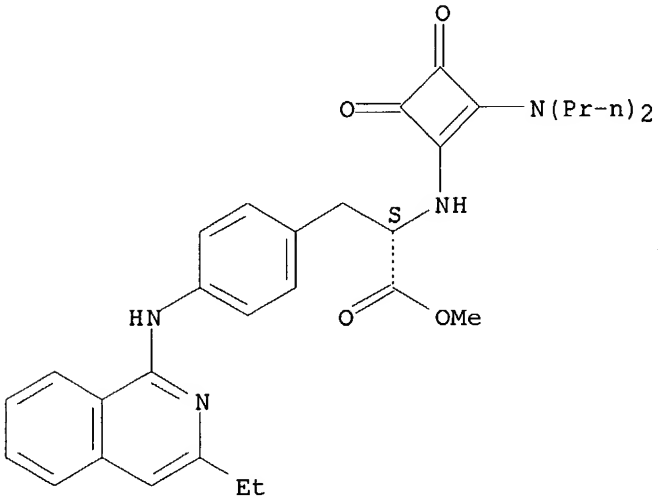
RN 378234-61-8 CAPLUS
CN L-Phenylalanine, N-[2-(diethylamino)-3,4-dioxo-1-cyclobuten-1-yl]-4-[(3-ethyl-1-isoquinolinyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



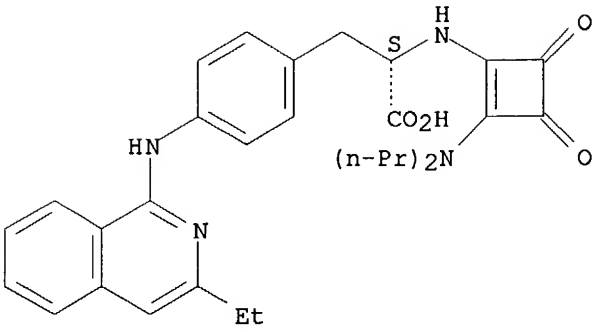
RN 378234-62-9 CAPLUS
CN L-Phenylalanine, N-[2-(dipropylamino)-3,4-dioxo-1-cyclobuten-1-yl]-4-[(3-ethyl-1-isoquinolinyl)amino]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



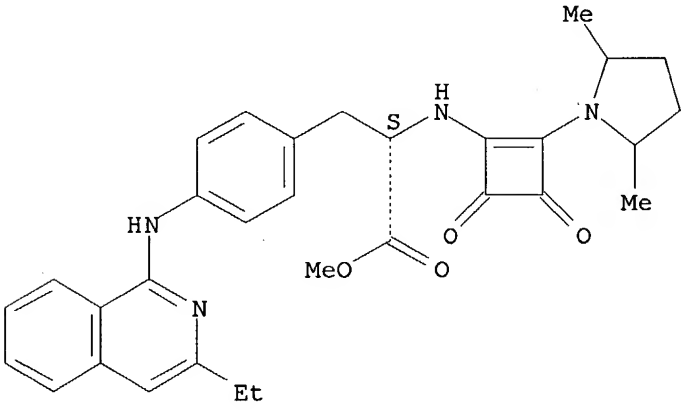
RN 378234-63-0 CAPLUS
CN L-Phenylalanine, N-[2-(dipropylamino)-3,4-dioxo-1-cyclobuten-1-yl]-4-[(3-ethyl-1-isoquinolinyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



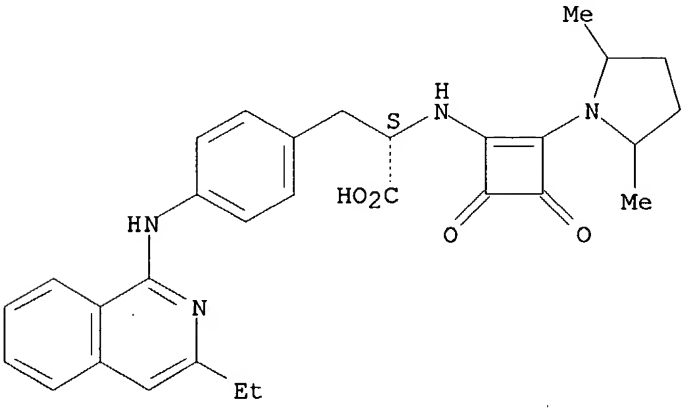
RN 378234-64-1 CAPLUS
CN L-Phenylalanine, N-[2-(2,5-dimethyl-1-pyrrolidinyl)-3,4-dioxo-1-cyclobuten-1-yl]-4-[(3-ethyl-1-isoquinolinyl)amino]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 378234-65-2 CAPLUS
CN L-Phenylalanine, N-[2-(2,5-dimethyl-1-pyrrolidinyl)-3,4-dioxo-1-cyclobuten-1-yl]-4-[(3-ethyl-1-isoquinolinyl)amino]- (9CI) (CA INDEX NAME)

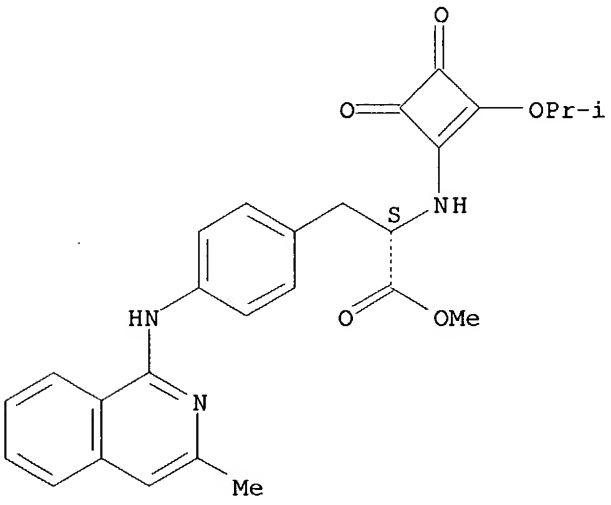
Absolute stereochemistry.



RN 378234-66-3 CAPLUS

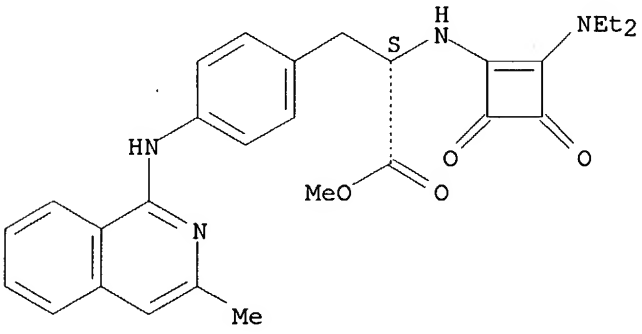
CN L-Phenylalanine, N-[2-(1-methylethoxy)-3,4-dioxo-1-cyclobuten-1-yl]-4-[(3-methyl-1-isoquinolinyl)amino]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



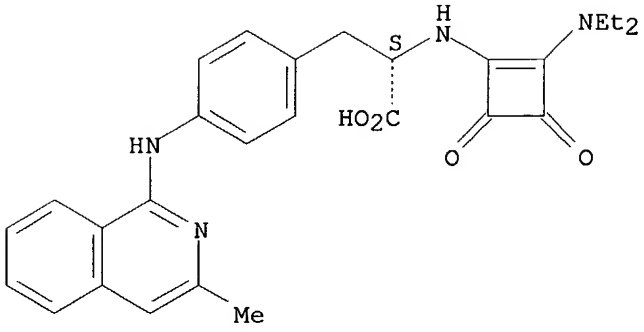
RN 378234-67-4 CAPLUS
CN L-Phenylalanine, N-[2-(diethylamino)-3,4-dioxo-1-cyclobuten-1-yl]-4-[(3-methyl-1-isoquinolinyl)amino]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



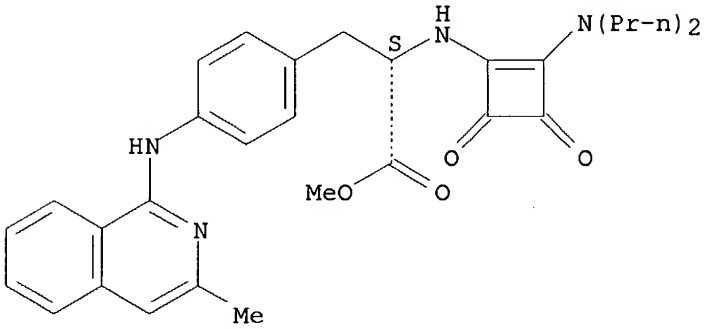
RN 378234-68-5 CAPLUS
CN L-Phenylalanine, N-[2-(diethylamino)-3,4-dioxo-1-cyclobuten-1-yl]-4-[(3-methyl-1-isoquinolinyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



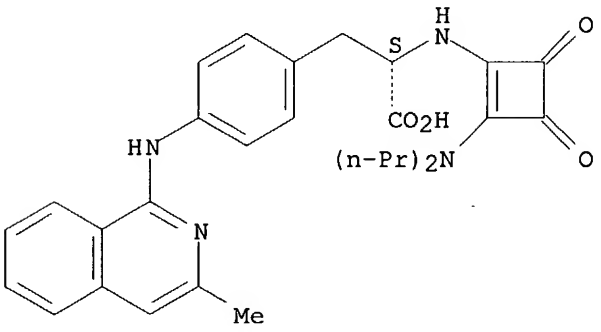
RN 378234-69-6 CAPLUS
CN L-Phenylalanine, N-[2-(dipropylamino)-3,4-dioxo-1-cyclobuten-1-yl]-4-[(3-methyl-1-isoquinolinyl)amino]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



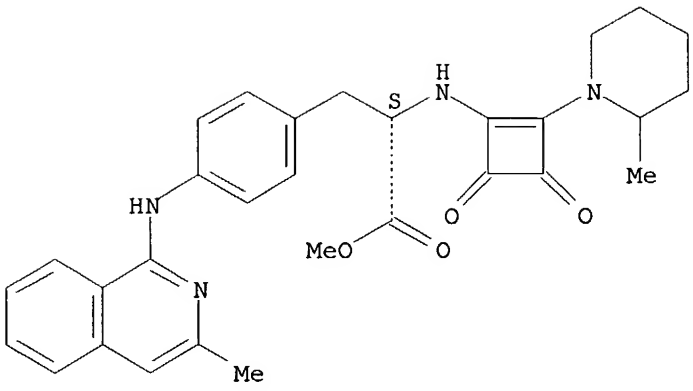
RN 378234-71-0 CAPLUS
CN L-Phenylalanine, N-[2-(dipropylamino)-3,4-dioxo-1-cyclobuten-1-yl]-4-[(3-methyl-1-isoquinolinyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 378234-72-1 CAPLUS
CN L-Phenylalanine, 4-[(3-methyl-1-isoquinolinyl)amino]-N-[2-(2-methyl-1-piperidinyl)-3,4-dioxo-1-cyclobuten-1-yl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.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S
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Me
HN
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MeO
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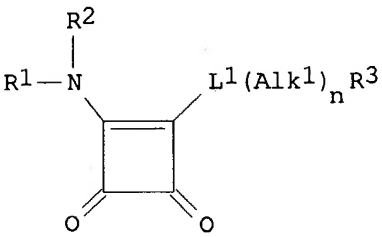
Me

L14 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:489353 CAPLUS
DOCUMENT NUMBER: 135:92389
TITLE: Preparation of squaric acid derivatives as integrin antagonists
INVENTOR(S): Langham, Barry John; Alexander, Rikki Peter; Head, John Clifford; Linsley, Janeen Marsha; Porter, John Robert; Archibald, Sarah Catherine; Warrellow, Graham John
PATENT ASSIGNEE(S): Celltech Chiroscience Limited, UK
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001047867	A1	20010705	WO 2000-GB4995	20001222
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2001020017	A1	20010906	US 2000-742038	20001221
US 6455539	B2	20020924		
EP 1244611	A1	20021002	EP 2000-987574	20001222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.:
GB 1999-30558 A 19991223
GB 2000-2872 A 20000208
GB 2000-28838 A 20001127
WO 2000-GB4995 W 20001222

OTHER SOURCE(S): CASREACT 135:92389; MARPAT 135:92389
GI



I

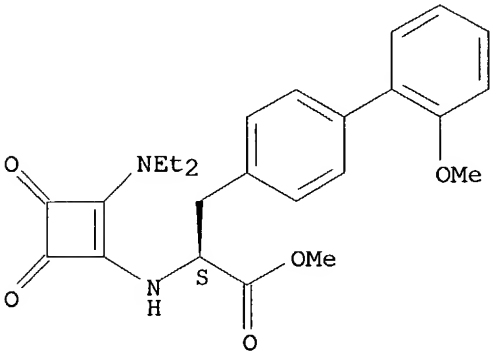
AB Preparation of squaric acid derivs. I are described (R1 = Ar1, Ar2Alk- in which Ar1 is an optionally substituted aromatic or heteroarom. group; Ar2 = optionally substituted phenylene or nitrogen-containing six-membered heteroarylene group; Alk = a chain -CH2CH(R)-, CH:C:C(R)-, (a) in which R is a carboxylic acid (-CO2H) or a derivative or biostere thereof; R2 = H, C1-6 alkyl; L1 = covalent bond or a linker atom or group; n = 0-1; Alk1 =

optionally substituted aliphatic chain; R3 = H, optionally substituted heteroaliph., cycloaliph., heterocycloaliph., polycycloaliph., heteropolycycloaliph., aromatic or heteroarom. group: and the salts, solvates, hydrates and N-oxides thereof). The compds. are able to inhibit the binding of integrins to their ligands and are of use in the prophylaxis and treatment of immune or inflammatory disorders, or disorders involving the inappropriate growth or migration of cells.

IT **348113-51-9P 348113-53-1P 348113-55-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of squaric acid derivs. as integrin antagonists)

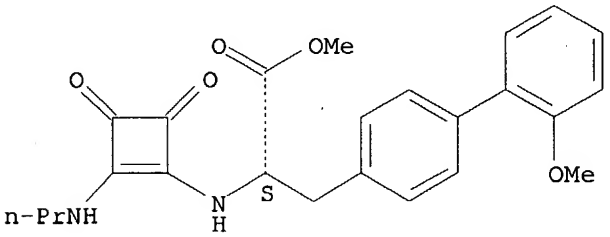
RN 348113-51-9 CAPLUS
CN [1,1'-Biphenyl]-4-propanoic acid, α-[[2-(diethylamino)-3,4-dioxo-1-cyclobuten-1-yl]amino]-2'-methoxy-, methyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



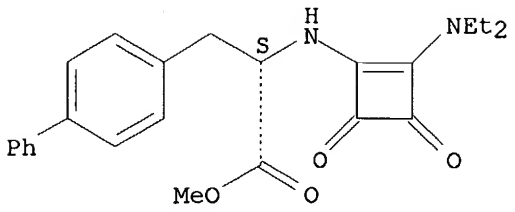
RN 348113-53-1 CAPLUS
CN [1,1'-Biphenyl]-4-propanoic acid, α-[[3,4-dioxo-2-(propylamino)-1-cyclobuten-1-yl]amino]-2'-methoxy-, methyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 348113-55-3 CAPLUS
CN [1,1'-Biphenyl]-4-propanoic acid, α-[[2-(diethylamino)-3,4-dioxo-1-cyclobuten-1-yl]amino]-, methyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

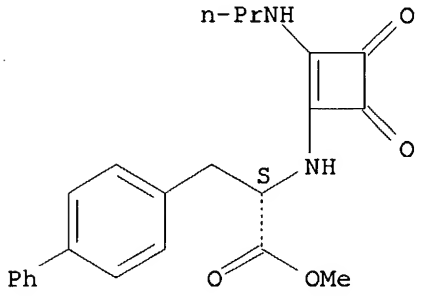


IT **348113-45-1P 348113-46-2P 348113-47-3P**
348113-48-4P 348113-49-5P 348113-50-8P
348113-52-0P 348113-54-2P 348113-56-4P
348113-60-0P 348113-61-1P 348113-62-2P
348113-63-3P 348113-64-4P 348113-65-5P
348113-66-6P 348113-67-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of squaric acid derivs. as integrin antagonists)

RN 348113-45-1 CAPLUS

CN [1,1'-Biphenyl]-4-propanoic acid, α-[[3,4-dioxo-2-(propylamino)-1-cyclobuten-1-yl]amino]-, methyl ester, (αS)- (9CI) (CA INDEX NAME)

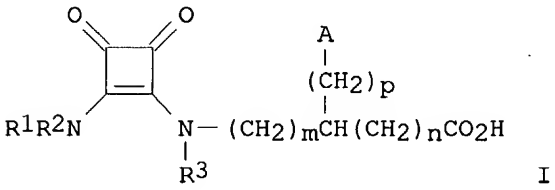
Absolute stereochemistry.



ER 12 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:909217 CAPLUS
DOCUMENT NUMBER: 134:56962
TITLE: Preparation of 3,4-diamino-3-cyclobutene-1,2-dione derivatives which inhibit leukocyte adhesion mediated by VLA-4
INVENTOR(S): Lombardo, Louis J.; Sabalski, Joan
PATENT ASSIGNEE(S): American Home Products Corp., USA
SOURCE: U.S., 21 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6166050	A	20001226	US 1999-458852	19991210

PRIORITY APPLN. INFO.: US 1998-155221P P 19981214
OTHER SOURCE(S): MARPAT 134:56962
GI



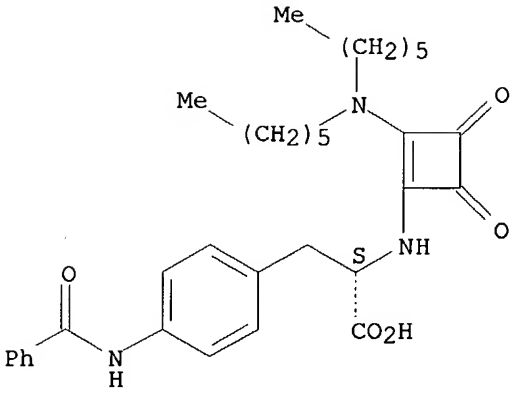
I

AB Diaminocyclobutenedione amino acid derivs. I (R1 = alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl; R2 = H, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl or R1R2N form a saturated or unsatd. heterocyclic ring; R3 = H, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl; A = aryl, heteroaryl; m, n, p = 0-3) were prepared for the treatment of inflammatory and autoimmune diseases. Thus, N-[2-(benzylamino)-3,4-dioxocyclobut-1-enyl]-L-phenylalanine, prepared by treatment of L-phenylalanine Me ester hydrochloride with 3,4-diethoxy-3-cyclobutene-1,2-dione and benzylamine and saponification, showed IC50 = 58 μM for binding of α4β1 integrin (VLA-4).

IT **274927-11-6P 274927-14-9P 274927-20-7P**
274927-22-9P 274927-24-1P 274927-26-3P
274927-29-6P 274927-31-0P 274927-33-2P
274927-38-7P 274927-51-4P 274927-53-6P
274927-56-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of diaminocyclobutenedione derivs. which inhibit leukocyte adhesion mediated by VLA-4)

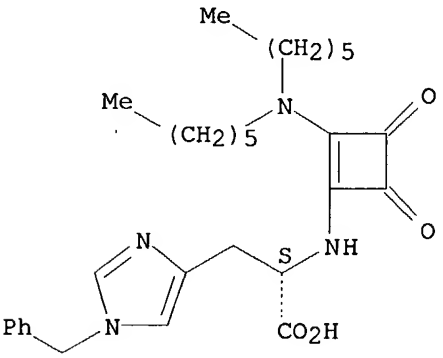
RN 274927-11-6 CAPLUS
CN L-Phenylalanine, 4-(benzoylamino)-N-[2-(dihexylamino)-3,4-dioxo-1-cyclobuten-1-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



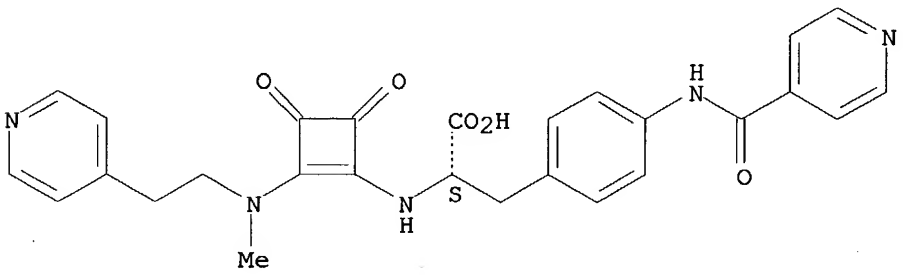
RN 274927-14-9 CAPLUS
CN L-Histidine, N-[2-(dihexylamino)-3,4-dioxo-1-cyclobuten-1-yl]-1-(phenylmethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



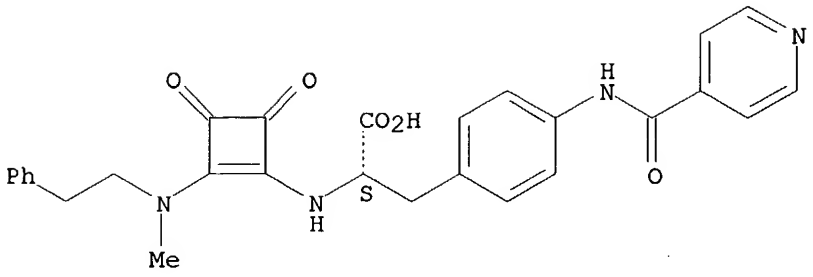
RN 274927-20-7 CAPLUS
CN L-Phenylalanine, N-[2-[methyl[2-(4-pyridinyl)ethyl]amino]-3,4-dioxo-1-cyclobuten-1-yl]-4-[(4-pyridinylcarbonyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



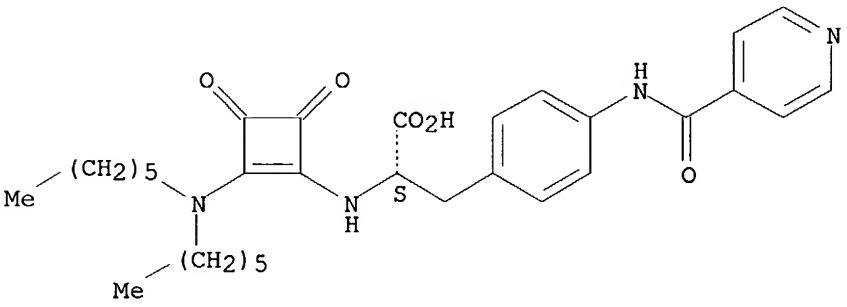
RN 274927-22-9 CAPLUS
CN L-Phenylalanine, N-[2-[methyl(2-phenylethyl)amino]-3,4-dioxo-1-cyclobuten-1-yl]-4-[(4-pyridinylcarbonyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



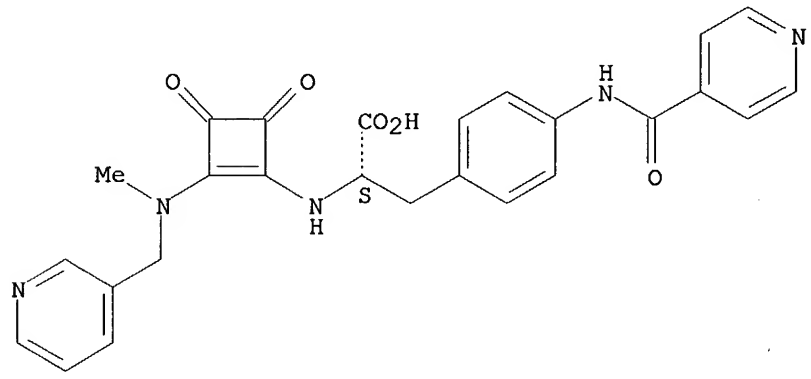
RN 274927-24-1 CAPLUS
CN L-Phenylalanine, N-[2-(dihexylamino)-3,4-dioxo-1-cyclobuten-1-yl]-4-[(4-pyridinylcarbonyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



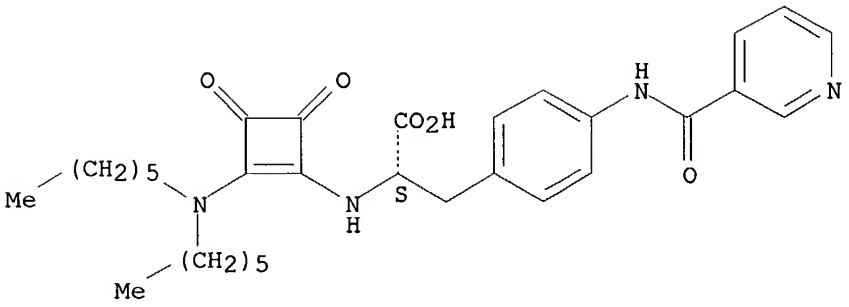
RN 274927-26-3 CAPLUS
CN L-Phenylalanine, N-[2-[methyl(3-pyridinylmethyl)amino]-3,4-dioxo-1-cyclobuten-1-yl]-4-[(4-pyridinylcarbonyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 274927-29-6 CAPLUS
CN L-Phenylalanine, N-[2-(dihexylamino)-3,4-dioxo-1-cyclobuten-1-yl]-4-[(3-pyridinylcarbonyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.


O
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S
(CH2)5
Me

L14 ANSWER 13 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:861644 CAPLUS
DOCUMENT NUMBER: 134:29705
TITLE: Preparation of squaric acid derivatives as cell adhesion molecules
INVENTOR(S): Langham, Barry John; Alexander, Rikki Peter; Head, John Clifford; Linsley, Janeen Marsha; Porter, John Robert; Archibald, Sarah Catherine; Warrelow, Graham John
PATENT ASSIGNEE(S): Celltech Chiroscience Limited, UK
SOURCE: PCT Int. Appl., 144 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000073260	A1	20001207	WO 2000-GB2020	20000526
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6518283	B1	20030211	US 2000-579317	20000525
EP 1181266	A1	20020227	EP 2000-935341	20000526
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2003500467	T2	20030107	JP 2000-621327	20000526
US 2003162799	A1	20030828	US 2002-319272	20021213

PRIORITY APPLN. INFO.:

GB 1999-12640	A	19990528
GB 2000-2858	A	20000208
US 2000-579317	A3	20000525
WO 2000-GB2020	W	20000526

OTHER SOURCE(S): MARPAT 134:29705
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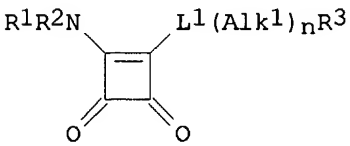


I

AB Squaric acid derivs. I [R1 is an integrin binding group; R2 is a hydrogen atom or a C1-6 alkyl group; L1 is a covalent bond or a linker atom or group; n = 0, 1; Alk1 is an optionally substituted aliphatic chain; R3 is H or an optionally substituted heteroaliph., cycloaliph., heterocycloaliph., polycycloaliph., polyheterocycloaliph., aromatic or heteroarom. group] and their salts, solvates, hydrates and N-oxides were prepared as inhibitors of

the binding of integrins to their ligands. Thus, treatment of Et (S)-3-(4-aminophenyl)-2-(tert-butoxycarbonylamino)propionate with 3,5-dichloro-4-pyridinecarboxylic acid, deprotection, reaction with 3,4-diisopropoxy-3-cyclobutene-1,2-dione, propylamination, and saponification afforded (S)-3-[4-(3,5-dichloro-4-pyridylcarboxamido)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid. Compds. of the invention in which R1 is an α4 integrin binding group generally have IC50 values <1 μM in the α4β1 and α4β7 assays.

IT **312292-12-9P**

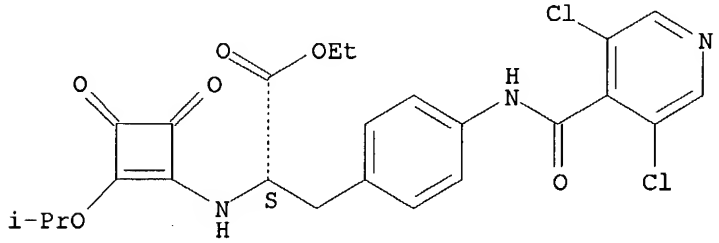
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(Preparation of squaric acid derivs. as cell adhesion mols.)

RN 312292-12-9 CAPLUS

CN L-Phenylalanine, 4-[[(3,5-dichloro-4-pyridinyl)carbonyl]amino]-N-[2-(1-methylethoxy)-3,4-dioxo-1-cyclobuten-1-yl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **312292-13-0P 312292-15-2P 312292-17-4P**
312292-19-6P 312292-21-0P 312292-23-2P
312292-24-3P 312292-25-4P 312292-40-3P
312292-45-8P 312292-46-9P 312292-48-1P
312292-67-4P 312292-68-5P 312292-86-7P
312293-01-9P 312293-02-0P

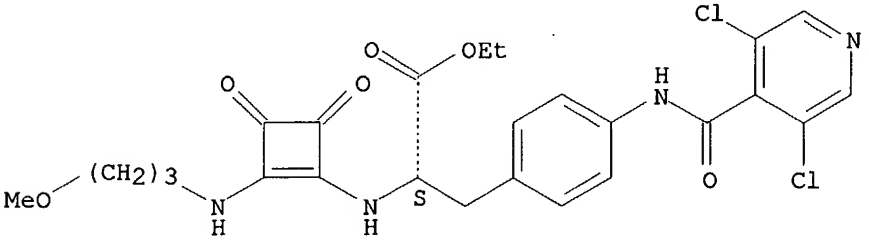
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of squaric acid derivs. as cell adhesion mols.)

RN 312292-13-0 CAPLUS

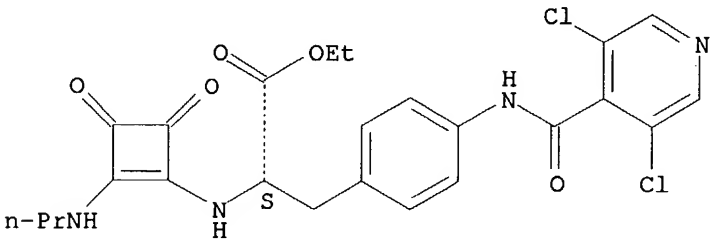
CN L-Phenylalanine, 4-[[(3,5-dichloro-4-pyridinyl)carbonyl]amino]-N-[2-[(3-methoxypropyl)amino]-3,4-dioxo-1-cyclobuten-1-yl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



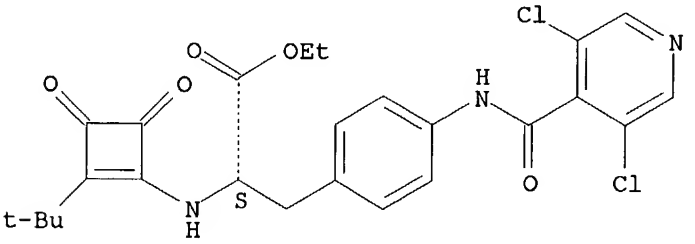
RN 312292-15-2 CAPLUS
CN L-Phenylalanine, 4-[[(3,5-dichloro-4-pyridinyl)carbonyl]amino]-N-[3,4-dioxo-2-(propylamino)-1-cyclobuten-1-yl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



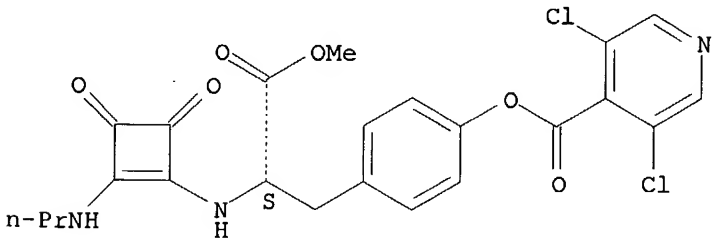
RN 312292-17-4 CAPLUS
CN L-Phenylalanine, 4-[[(3,5-dichloro-4-pyridinyl)carbonyl]amino]-N-[2-(1,1-dimethylethyl)-3,4-dioxo-1-cyclobuten-1-yl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



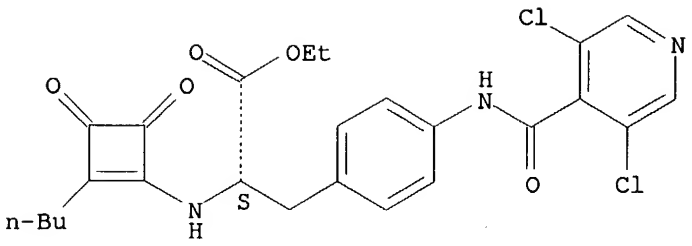
RN 312292-19-6 CAPLUS
CN L-Tyrosine, N-[3,4-dioxo-2-(propylamino)-1-cyclobuten-1-yl]-, methyl ester, 3,5-dichloro-4-pyridinecarboxylate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



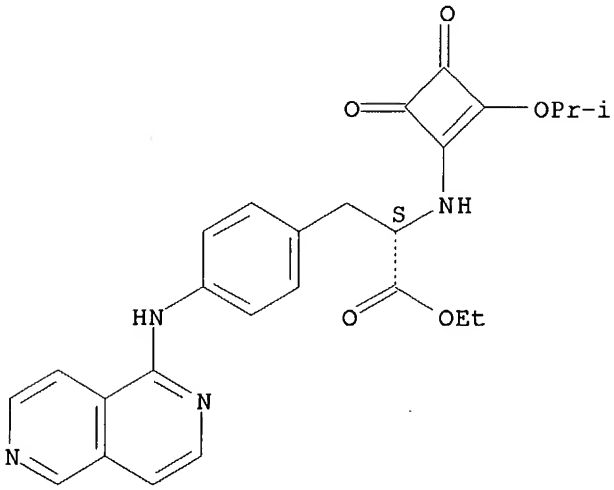
RN 312292-21-0 CAPLUS
CN L-Phenylalanine, N-(2-butyl-3,4-dioxo-1-cyclobuten-1-yl)-4-[[(3,5-dichloro-4-pyridinyl)carbonyl]amino]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



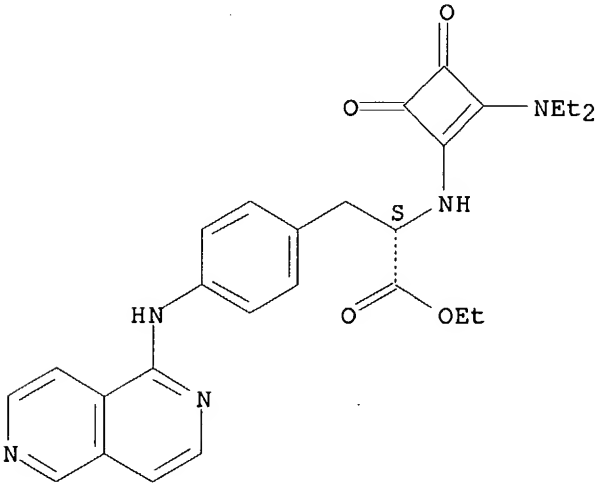
RN 312292-23-2 CAPLUS
CN L-Phenylalanine, N-[2-(1-methylethoxy)-3,4-dioxo-1-cyclobuten-1-yl]-4-(2,6-naphthyridin-1-ylamino)-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 312292-24-3 CAPLUS
CN L-Phenylalanine, N-[2-(diethylamino)-3,4-dioxo-1-cyclobuten-1-yl]-4-(2,6-naphthyridin-1-ylamino)-, ethyl ester (9CI) (CA INDEX NAME)

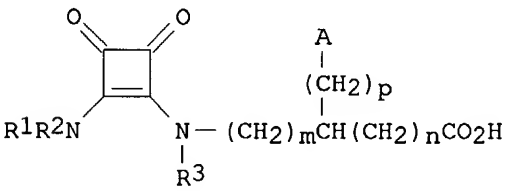
Absolute stereochemistry.



T 2004 ACS on STN
ACCESSION NUMBER: 2000:421084 CAPLUS
DOCUMENT NUMBER: 133:43808
TITLE: Preparation of 3,4-diamino-3-cyclobutene-1,2-dione derivatives which inhibit leukocyte adhesion mediated by VLA-4
INVENTOR(S): Lombardo, Louis John; Sabalski, Joan E.
PATENT ASSIGNEE(S): American Home Products Corporation, USA
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000035855	A1	20000622	WO 1999-US29369	19991210
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
BR 9916211	A	20010911	BR 1999-16211	19991210
EP 1140792	A1	20011010	EP 1999-967265	19991210
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: US 1998-211183 A 19981214
WO 1999-US29369 W 19991210
OTHER SOURCE(S): MARPAT 133:43808
GI



I

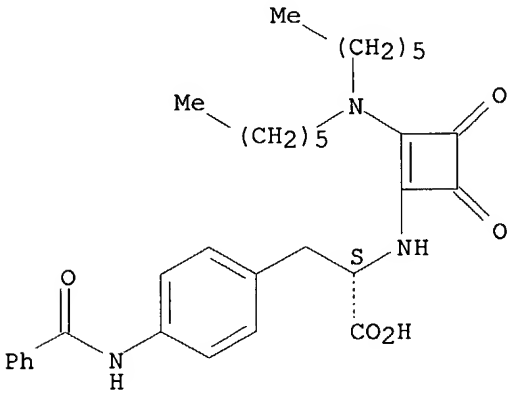
AB Diaminocyclobutenedione amino acid derivs. I (R1 = alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl; R2 = H, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl or R1R2N form a saturated or unsatd. heterocyclic ring; R3 = H, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl; A = aryl, heteroaryl; m, n, p = 0-3) were prepared for the treatment of inflammatory and autoimmune diseases. Thus, N-[2-(benzylamino)-3,4-dioxocyclobut-1-enyl]-L-phenylalanine, prepared by treatment of L-phenylalanine Me ester hydrochloride with 3,4-diethoxy-3-cyclobutene-1,2-dione and benzylamine and saponification, showed IC50 for binding of the α4β1 integrin (VLA-4).

IT **274927-11-6P 274927-14-9P 274927-20-7P**
274927-22-9P 274927-24-1P 274927-26-3P
274927-29-6P 274927-31-0P 274927-33-2P

274927-38-7P 274927-51-4P 274927-53-6P
274927-56-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of diaminocyclobutenedione derivs. which inhibit leukocyte adhesion mediated by VLA-4)

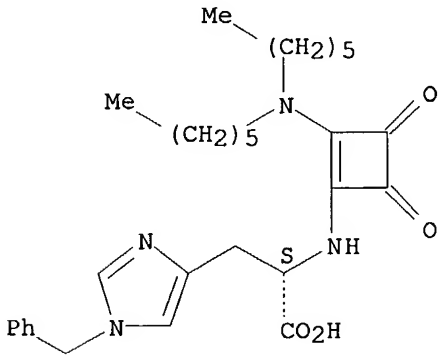
RN 274927-11-6 CAPLUS
CN L-Phenylalanine, 4-(benzoylamino)-N-[2-(dihexylamino)-3,4-dioxo-1-cyclobuten-1-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



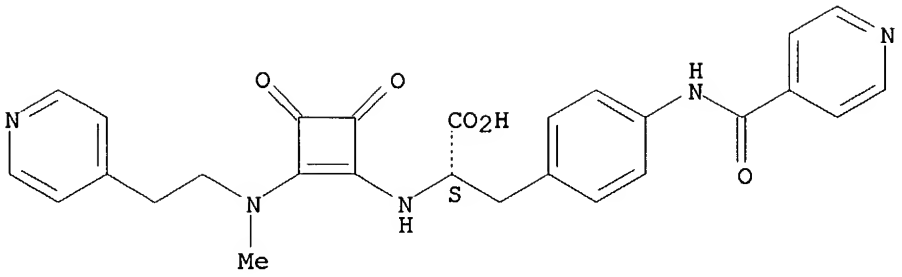
RN 274927-14-9 CAPLUS
CN L-Histidine, N-[2-(dihexylamino)-3,4-dioxo-1-cyclobuten-1-yl]-1-(phenylmethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



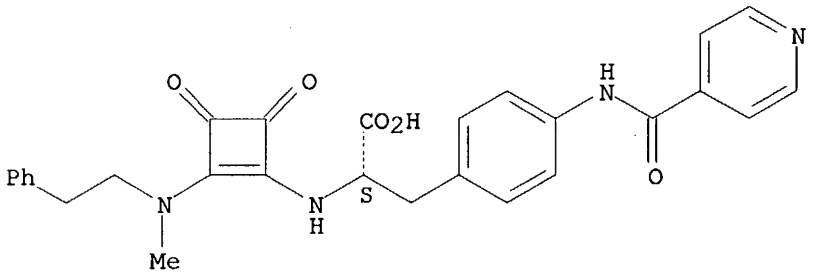
RN 274927-20-7 CAPLUS
CN L-Phenylalanine, N-[2-[methyl[2-(4-pyridinyl)ethyl]amino]-3,4-dioxo-1-cyclobuten-1-yl]-4-[(4-pyridinylcarbonyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



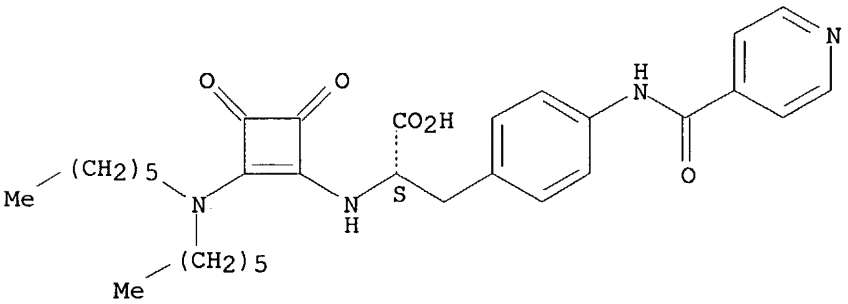
RN 274927-22-9 CAPLUS
CN L-Phenylalanine, N-[2-[methyl(2-phenylethyl)amino]-3,4-dioxo-1-cyclobuten-1-yl]-4-[(4-pyridinylcarbonyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



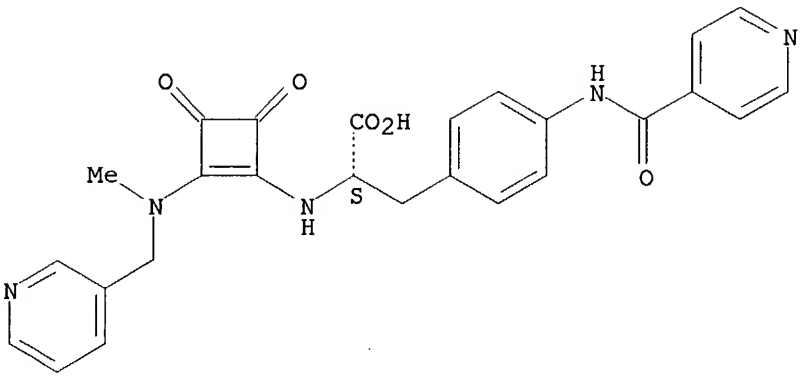
RN 274927-24-1 CAPLUS
CN L-Phenylalanine, N-[2-(dihexylamino)-3,4-dioxo-1-cyclobuten-1-yl]-4-[(4-pyridinylcarbonyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



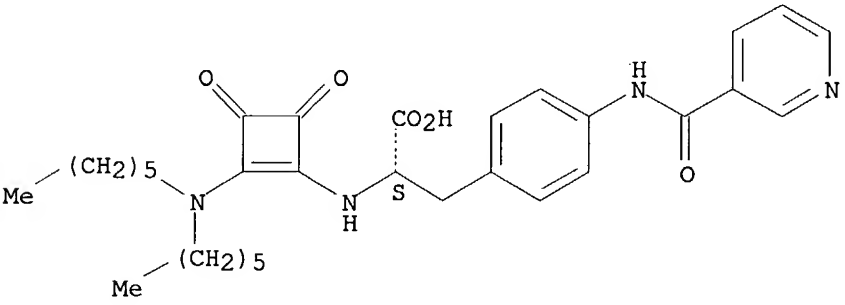
RN 274927-26-3 CAPLUS
CN L-Phenylalanine, N-[2-[methyl(3-pyridinylmethyl)amino]-3,4-dioxo-1-cyclobuten-1-yl]-4-[(4-pyridinylcarbonyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



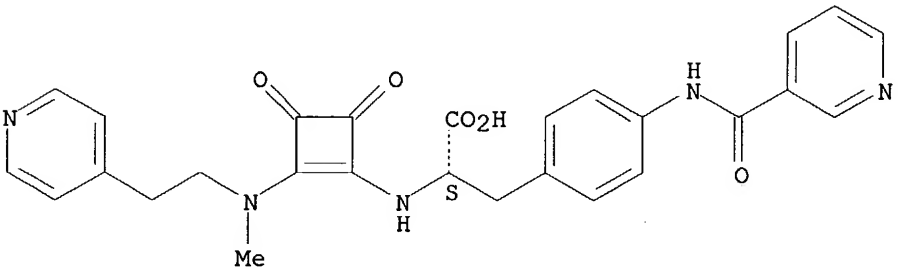
RN 274927-29-6 CAPLUS
CN L-Phenylalanine, N-[2-(dihexylamino)-3,4-dioxo-1-cyclobuten-1-yl]-4-[(3-pyridinylcarbonyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 274927-31-0 CAPLUS
CN L-Phenylalanine, N-[2-[methyl[2-(4-pyridinyl)ethyl]amino]-3,4-dioxo-1-cyclobuten-1-yl]-4-[(3-pyridinylcarbonyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 274927-33-2 CAPLUS
CN L-Phenylalanine, N-[2-[methyl(3-pyridinylmethyl)amino]-3,4-dioxo-1-